# GLOBAL MORTALITY ATTRIBUTABLE TO ALCOHOLIC CARDIOMYOPATHY

## Dissertation

for the degree of
Doctor rerum naturalium
(Dr. rer. nat.)

presented to the
School of Science
Technische Universität Dresden

by

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Submitted on March 13, 2020
Defended on July 2, 2020

The work for this dissertation was performed at the Institute for Clinical Psychology and Psychotherapy, TU Dresden between January 2016 and December 2019.

# Statement for a publication-based dissertation

The proposed dissertation has been prepared as self-contained work and is based on three peer-reviewed publications. The contribution of the doctoral candidate to each of the underlying publications is described below.

**Study I, chapter 4**

Manthey, J., Imtiaz, S., Neufeld, M., Rylett, M., & Rehm, J. (2017). Quantifying the global contribution of alcohol consumption to cardiomyopathy. *Population Health Metrics, 15*(20). doi:10.1186/s12963-017-0137-1 (IF = 2.3)

JM developed the study concept and study design under the supervision of JR. SI, MN, MR, and JR performed data collection and JM performed the data analysis. JM and JR drafted the manuscript, and all remaining authors provided critical revisions.

**Study II, chapter 5**

Manthey, J., Probst, C., Rylett, M., & Rehm, J. (2018). National, regional and global mortality due to alcoholic cardiomyopathy in 2015. *Heart, 104*(20), 1663-1669. doi:10.1136/heartjnl-2017-312384 (IF = 5.4)

JM developed the study concept and study design under the supervision of JR. JM and MR performed data collection and JM performed the data analysis. JM drafted the manuscript, and CP, MR and JR provided critical revisions.

**Study III, chapter 6**

Manthey, J., & Rehm, J. (2019). Mortality from alcoholic cardiomyopathy: Exploring the gap between estimated and civil registry data. *Journal of Clinical Medicine, 8*(8). doi:10.3390/jcm8081137 (IF = 5.6)

JM developed the study concept and study design under the supervision of JR. JM performed data collection and the data analysis. JM drafted the manuscript, and JR provided critical revisions.

None of the above publications have been or are intended to be used for other dissertations.

# Contents

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# Abbreviations

| | |
|---|---|
| **AAF** | alcohol-attributable fraction |
| **ACM** | alcoholic cardiomyopathy |
| **APC** | alcohol *per capita* consumption (among adults) |
| **AUD** | alcohol use disorder |
| **C17** | neoplasm of small intestine |
| **CM** | cardiomyopathy |
| **CI** | confidence interval |
| **CVD** | cardiovascular diseases |
| **F10** | ICD-10 section for alcohol-related diseases |
| **F12** | ICD-10 disease code for alcohol dependence |
| **GBD** | Global Burden of Disease |
| **GDP** | gross domestic product |
| **HED** | heavy episodic drinking |
| **HF** | heart failure |
| **I20-I25** | ICD-10 section for ischemic heart disease |
| **I42** | ICD-10 section for cardiomyopathy |
| **I42.6** | ICD-10 section for alcoholic cardiomyopathy |
| **I85** | ICD-10 disease code esophageal varices |
| **ICD** | International Classification of Diseases |
| **ICD-10** | Tenth Revision of the International Classification of Diseases |
| **ICD-11** | Eleventh Revision of the International Classification of Diseases |
| **IRR** | Incidence rate ratio |
| **K29.2** | ICD-10 disease code for alcoholic gastritis |
| **PAF** | population-attributable fraction |
| **PPP** | purchasing power parity |
| **Q86** | ICD-10 disease code for fetal alcohol syndrome |
| **RR** | relative risk |
| **WHO** | World Health Organization |

# Abstract

**Introduction** Globally, around 2.6 billion people have consumed alcohol in 2017. In the same year, nearly 3 million or 5% of all deaths were attributable to alcohol consumption, the majority of which were non-communicable diseases, such as cancer, digestive and cardiovascular diseases. Chronic heavy alcohol consumption in particular causes harm to the cardiovascular system and is linked to an elevated risk on the occurrence of ischemic heart diseases and cardiomyopathies. The latter constitutes a heterogeneous group of cardiovascular diseases, which can generally be characterized by a weakened heart muscle. The causal link between chronic heavy alcohol consumption and cardiomyopathy has long been recognized, with the Tenth Revision of the International Classification of Diseases (ICD-10) listing alcoholic cardiomyopathy (ACM) as a fully alcohol-attributable diagnosis. For a few, predominately high-income countries, civil registries provide valuable information of ACM mortality. However, for the majority of countries and global population, the cardiomyopathy burden attributable to alcohol consumption needs to estimated. Established methods for estimating alcohol-attributable fractions (AAF), i.e. proportion of an outcome which could be avoided in a scenario of zero alcohol consumption, could not be applied for cardiomyopathy as the link between alcohol consumption levels and risk of cardiomyopathy could not be specified. Accordingly, a global assessment of the contribution of alcohol consumption to the disease burden from cardiomyopathy was lacking.

**Aims and objectives** First, to develop methods for estimating the contribution of alcohol consumption to cardiomyopathy that can be used globally (study I). Second, to apply the method developed in study I to estimate the global mortality from ACM (study II). Third, to assess differences between this method and an alternative method for estimating the contribution of alcohol consumption to cardiomyopathy proposed during pursuit of these aims (study III).

**Design** Statistical modelling study with country-level data as unit of analyses.

Study I. Based on mortality data from civil registries, the proportion of deaths from ACM among deaths from any cardiomyopathy (=AAF) was used as proxy for the link between alcohol consumption and cardiomyopathy. To generalize this link to countries without available civil registry data, associations of population alcohol exposure and registered AAF were established. Cardiomyopathy deaths that are attributable to alcohol use were quantified in those countries with available registry data.

Study II. For countries without available civil registry data, ACM mortality was estimated using population alcohol exposure data based on the methods from study I. As a result, national, regional and global estimates of the mortality attributable to ACM were obtained for the year 2015.

Study III. In the alternative method developed by the Global Burden of Disease (GBD) study team, the contribution of alcohol consumption to cardiomyopathy was estimated taking into account that actual ACM deaths may be incorrectly coded as so-called garbage codes (disease codes that do not accurately describe the underlying cause of death). In the alternative method, garbage codes were redistributed to both cardiomyopathy and ACM using statistical procedures. The underlying assumptions for the redistribution of garbage codes were examined by comparing registered and estimated ACM mortality data taking into account the distribution of alcohol exposure.

**Data sources** Data on population alcohol exposure (alcohol *per capita* consumption, prevalence of heavy episodic drinking, prevalence of alcohol use disorders) were sourced from publicly available World Health Organization (WHO) data bases. As outcome data, sex-specific mortality counts from different disease groups (ACM, any cardiomyopathy, and selected garbage codes) were obtained at the country level from three different sources: First, WHO mortality data base, which provide civil registry mortality data on nearly half of all member states, coded according to the ICD-10. Second and third, 'Global Health Estimates' and 'GBD Results Tool' data bases, which provide complete and consistent mortality estimates aggregated into larger disease groups for all WHO member states. Data on covariates were obtained from the United Nations and the World Bank.

**Statistical analyses** In study I, the dependent variable – AAF for cardiomyopathy – was calculated by dividing deaths from ACM by deaths from any cardiomyopathy, based on civil registry data from *N*=52 countries. Taking into account country-specific crude mortality rates of ACM, AAF were modeled in two-step sex-specific regression analyses using population alcohol exposure as covariate. AAF were estimated for the same set of *N*=52 countries, in addition to *N*=43 countries without civil registry data. Estimated AAF were compared to registered AAF available for *N*=52 countries.

In study II, the global mortality of ACM was estimated by combining civil registry ACM mortality data for *N*=91 countries and estimated ACM mortality for *N*=99 countries without available civil registry data. For the latter set of countries, ACM mortality data were calculated by estimating AAF based on the methodology outlined in the first study and subsequently applied to all cardiomyopathy deaths. As a proxy for under-reporting of ACM in civil registries, estimated ACM deaths were compared to registered ACM deaths for *N*=91 countries.

In study III, ACM mortality estimates from the GBD study were compared against registered ACM mortality data for *N*=77 countries, aiming to test underlying assumptions for redistribution of garbage-coded deaths in the alternative method. For this purpose, descriptive statistics and Pearson correlations were used to assess the association of estimated and registered deaths and to examine consistency of estimates with population alcohol exposure.

**Results** In study I, population alcohol exposure and ACM mortality were closely linked (spearman correlation=0.7), supporting the proposed modelling strategy. For *N*=95 countries, the AAF for cardiomyopathy was estimated at 6.9% (95% confidence interval (CI): 5.4-8.4%), indicating that one in 14 of all cardiomyopathy deaths were attributable to alcohol in the year 2013 or the last available year. The findings were robust, with 78% of all estimated AAF deviating less than 5% from registered AAF.

In study II, it was estimated that 25,997 (95% CI: 17,385-49,096) persons died from ACM in 2015 globally, with 76.0% of ACM deaths being located in Russia. Globally, 6.3% (95% CI: 4.2-11.9%) of all deaths from cardiomyopathy were estimated to be caused by alcohol. Furthermore, indications of underreporting in civil registration mortality data were found, with two out of three global ACM deaths being possibly misclassified.

In study III, findings suggested that only one in six ACM deaths were correctly coded in civil registries of *N*=77 countries. However, the algorithm accounting for misclassifications in the GBD study was not aligned with population alcohol exposure, which has led to implausibly high ACM mortality estimates for people aged 65 years or older. Specifically, registered and estimated ACM mortality rates diverged in the elderly, which was corroborated with decreasing correlations in these age groups.

**Conclusions** For countries without civil registry data, the contribution of alcohol consumption to mortality from cardiomyopathy could be quantified using population alcohol exposure and estimated mortality data for any cardiomyopathy. The proposed method was adapted by the WHO in 2018, allowing for a more complete picture of the alcohol-attributable global disease burden for nearly 200 countries. Notably, ACM mortality was hardly present in countries with low to moderate alcohol consumption levels, corroborating that ACM is the result of sustained and very high alcohol consumption levels.

In civil registries, at least two out of three ACM deaths are misclassified, thus, presented mortality figures are likely underestimated. As with other alcohol-attributable diseases, misclassification of ACM mortality is a systematic phenomenon, which may be caused by low resources, lacking standards and severe stigma associated with alcohol use disorders. With transition from ICD-10 to ICD-11, new methods will be required as ACM will not remain a unique diagnosis in the new classificatory system. Future methods should account for mortality misclassifications by redistributing garbage codes while taking into consideration the distribution of alcohol exposure. Further, measures to reduce stigma may improve diagnostic accuracy for ACM and other alcohol-attributable diseases. This will not only improve public health statistics but also – and more importantly – improve health prospects of persons with heavy alcohol consumption.

# 1 Introduction

## 1.1 Global extent of alcohol use

Globally, about every second adult has consumed alcohol in 2017, which sums up to 2.6 billion people being exposed to a major risk factor for disease burden (Manthey et al., 2019). Alcohol *per capita* consumption (APC), measured as the average intake of pure alcohol within one year per adult, amounted to 6.5 liters, which is equivalent to a daily consumption of a small can of beer (350ml) or a glass of wine (125ml). Considering that all alcohol is only drunk by current drinkers, which make up about half of the adult population, the average global alcohol intake among drinkers was 13.7 liters in 2017, which corresponds to a daily consumption of about 750ml beer or 270ml wine.

There is a substantial regional variation in both prevalence of drinking and drinking levels. In the Eastern Mediterranean region, only one in twenty adults drink alcohol, whereas in Europe, Western Pacific, and the Americas two out of three adults reported drinking alcohol in 2017. With regard to drinking levels among drinkers, a different regional pattern can be observed, with the highest intake being recorded in Sub-Saharan and South Asian countries, as well as in Eastern and Central Europe (see **Figure 1.1**).

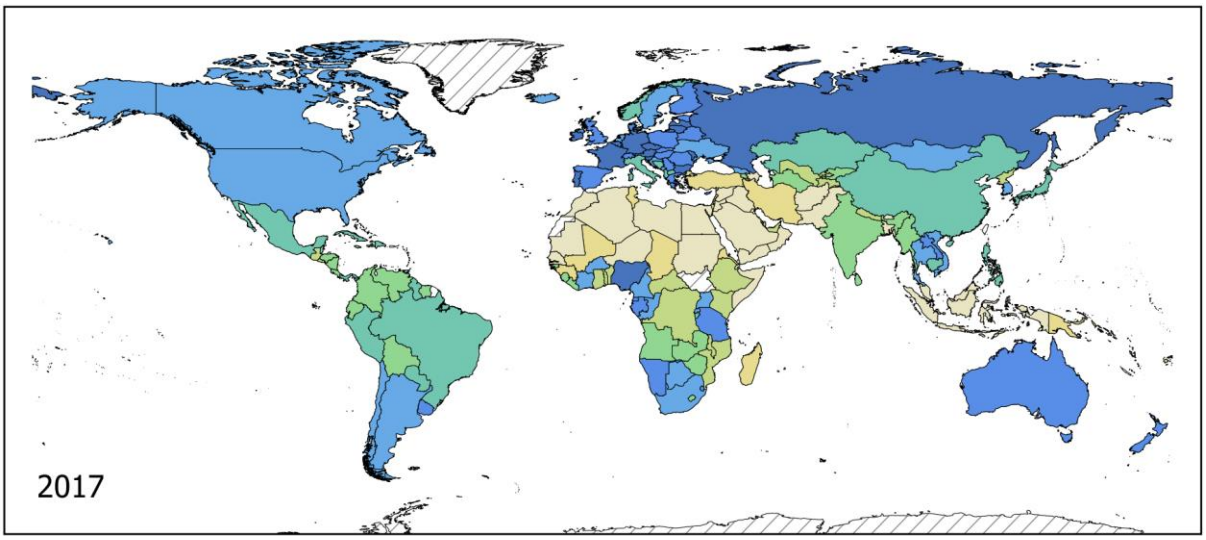


**Figure 1.1** Global alcohol consumption in pure liter alcohol per adult in the year 2017 (taken from (Manthey et al., 2019))

In recent years, per-capita alcohol consumption has slightly fallen in Europe, mainly due to reductions in Eastern European countries following the implementation of effective alcohol control policies (Neufeld & Rehm, 2013; Rehm, Manthey, Shield, & Ferreira-Borges, 2019). In contrast, stark increases have been observed in other parts of the world, especially in South-, South-East, and East Asia. These trends largely reflect an increased affordability of alcoholic beverages in a substantial share of the world population driven by rising economic wealth. Taken together, global alcohol consumption has steadily grown in the past decades and is projected to grow further in the next decade (Manthey et al., 2019).

## 1.2 Alcohol-attributable disease burden

The high global exposure to alcohol consumption is also reflected in a considerable extent of the corresponding burden from mortality and morbidity, i.e. disease burden. In addition to fully alcohol-attributable diseases such as alcohol use disorders (AUDs), fetal alcohol syndrome, and alcoholic cardiomyopathy (ACM), there are dozens of codes in the Tenth Revision of the International Classification of Diseases (ICD-10, (World Health Organization, 1993)), which are causally linked to alcohol consumption, resulting in partial attribution. Broadly, the detrimental effects of alcohol consumption were identified for both non-communicable and communicable diseases, as well as injuries, most importantly for cancers, cardiovascular diseases (CVD), diseases of the digestive and nervous system, and motor vehicle accidents (Rehm, Gmel, et al., 2017). Summing up all alcohol-attributable deaths across these disease and injury categories resulted in a global death toll of 2.8 million people in 2017, which corresponded to 5% of all age-standardized deaths (Institute for Health Metrics and Evaluation, 2019). Compared to other risk factors contributing to the burden of disease (e.g. high systolic blood pressure, tobacco use), alcohol consumption ranked 7$^{th}$ globally in 2017. However, among males only, alcohol use ranked 4$^{th}$ globally and was even the most important risk factor for disease burden in males aged 15 to 49 (Stanaway et al., 2018).

As the alcohol-attributable mortality is closely linked to alcohol exposure, a roughly similar pattern of mortality can be observed across world regions: In the Eastern Mediterranean Region, less than 1% of age-standardized deaths were attributable to alcohol consumption, whereas in the European Region, the alcohol-attributable proportion of all age-standardized deaths is 8%. Similarly, the relative alcohol-attributable mortality burden has decreased in Europe, but increased in South-, South-East, and East Asia since 2010 (Institute for Health Metrics and Evaluation, 2019).

The extent of alcohol-attributable morbidity and mortality has not only been used to illustrate the disease burden to society, but has further been incorporated in various health economics studies such as cost-of-illness and cost-effectiveness studies. Cost-of-illness studies conducted in high-income (Mohapatra, Patra, Popova, Duhig, & Rehm, 2010) and middle-income countries (e.g. (Ranaweera et al., 2018; Thavorncharoensap et al., 2010)) suggest that alcohol consumption make up between 1% and 2% of the gross domestic product (GDP). Further, cost-benefit studies also refer to measures of alcohol-attributable diseases in estimating the saved costs arising from avoided morbidity and mortality (e.g. fewer hospitalizations, higher productivity), which are expressed as monetary benefits arising from interventions. Those alcohol interventions, for which the costs of implementation represent only a small share of the monetary benefits, are the so-called best buys (Chisholm et al., 2018). These are promoted by the WHO (World Health Organization, 2018b) and implemented in a growing number of countries (e.g. Brazil, Russia, India, China, South Africa: (Rabiee, Agardh, Coates, Allebeck, & Danielsson, 2017), Russia: (Neufeld & Rehm, 2013), Lithuania: (Rehm, Stelemekas, & Badaras, 2019)).

In summary, accurate measures of the alcohol-attributable disease burden not only represent the foundation for classic epidemiological research such as the Global Burden of Disease (GBD) Study but also impact provision of healthcare programs at the national and international level. For instance, acknowledging the substantial degree of avoidable disease burden caused by alcohol, all WHO member states have agreed on reducing alcohol consumption by 10% until 2025 (World Health Organization, 2013).

## 1.3 Estimating the alcohol-attributable burden

Given the direct policy impact, it is vital that estimates of alcohol-attributable harm are based on a sound methodology. In fact, the methodology has been improved considerably in recent years, as reflected in sub-group estimations (Probst, Parry, Wittchen, & Rehm, 2018) and refinement of methods for alcohol-attributable injuries (Ye et al., 2019)). In a 2017 monograph, more than 50 ICD-10 codes fully attributable to alcohol in addition to 35 disease categories and several injury groups partially impacted by alcohol consumption have been identified (Rehm, Gmel, et al., 2017). In **Table 1.1**, all disease and injury groups with known links to alcohol consumption are portrayed. In addition to these partially impacted diseases and injuries, there are 53 codes in the ICD-10 that are fully attributable to alcohol consumption, such as the alcohol-related diseases (F10), ACM (I42.6), alcoholic gastritis (K29.2), and fetal alcohol syndromes (Q86).

**Table 1.1** Disease groups partially attributable to alcohol consumption according to Rehm, Gmel, et al. (2017)

| **Overall disease/ injury groups** | **Diseases/injuries causally impacted by alcohol consumption** |
|---|---|
| Infectious diseases | Tuberculosis; HIV/AIDS; Other sexually transmitted diseases; Lower respiratory infections |
| Cancers | Lip and oral cavity; Nasopharynx; Other pharynx; Esophagus; Stomach; Colon and rectum; Liver; Pancreatic; Larynx; Trachea, bronchus, and lung; Female breast; Other |
| Diabetes mellitus | Diabetes mellitus |
| Neuropsychiatric disorders | Alzheimer's disease and other dementias; Unipolar depressive disorders; Epilepsy |
| Cardiovascular diseases | Hypertensive heart disease; Ischemic heart disease; Cardiomyopathy; Atrial fibrillation and flutter; Heart failure; Ischemic stroke; Hemorrhagic and other non-ischemic stroke; Esophageal varices |
| Gastrointestinal diseases | Cirrhosis of the liver; Gall bladder and bile duct disease; Pancreatitis; Other digestive diseases |
| Other disease categories | Psoriasis; Abortion; Preterm birth complications |
| Injuries | Motor vehicle collisions; Unintentional injuries; Intentional injuries |

*How to determine the contribution of alcohol consumption for a given disease?*

For disease and injury codes that are only partially impacted by alcohol consumption, the contribution of alcohol is not captured in the diagnostic criteria, which makes it difficult to quantify the impact of alcohol. The following two examples illustrate the problem: It is reasonable that all cases of alcohol dependence (F12) could be avoided if no person drank any alcohol. For ischemic heart disease (I20-I25), however, the number of cases attributable to alcohol consumption cannot be inferred from the diagnosis, as it does not presuppose any use of alcohol whatsoever.

One way to approximate the contribution of alcohol would be to consider secondary or contributory diagnoses indicating alcohol use, such as any F10 code (White, Castle, Hingson, & Powell, 2020). However, this approach has three important downsides: First, this approach would require comprehensive vital statistics including data on multiple cause of death, which is only available for few high-income or upper middle-income countries. Second, it requires reliable diagnoses of alcohol-related disorders. However, this assumption is problematic as alcohol dependence is underdiagnosed by physicians (Rehm et al., 2015), likely because alcohol dependence is a highly stigmatized subject as perceived not only by general practitioners (Hanschmidt et al., 2017), but also by the general population (Schomerus et al., 2011). Third, this approach would mainly capture heavy users as the vast majority of drinkers with low or moderate drinking levels are never diagnosed with an alcohol-related diagnosis. However, as even low levels of alcohol use can impact the risk for certain diseases (for ischemic heart disease, see (Ronksley, Brien, Turner, Mukamal, & Ghali, 2011)), a too narrow focus on people with F10 diagnoses will likely underestimate the contribution of alcohol. Fourth, the protective effect of alcohol consumption, i.e. a reduced risk of disease onset at certain drinking levels, could not be captured as avoided cases are not registered in the healthcare system by definition.

Thus, in order to accurately estimate the contribution of alcohol for given disease groups, a methodology embedded in the comparative risk assessment framework has been developed (Murray, Lopez, World Health Organization, World Bank, & Harvard School of Public Health, 1996) and ever since routinely applied (e.g. (World Health Organization, 2014, 2018b)). Based on this methodology, so called population-attributable fractions (PAFs) are calculated, which usually range between 0% and 100% and denote the share of cases, which could be avoided in a counterfactual scenario (Levin, 1953; Leviton, 1973). Negative PAFs, i.e. < 0%, can also be estimated – they indicate how many cases could be avoided due to beneficial effects of the studied risk factor. For alcohol, the PAFs are commonly termed alcohol-attributable fractions (AAF) and the counterfactual scenario is a completely alcohol-free world (Rehm et al., 2001).

**Equation 1.1:**

$$PAF = \frac{P\,(RR-1)}{1+P(RR-1)}$$

In general, the approach to calculate AAF follows the same concept as stipulated by Levin, but the AAF estimations have been refined considerably in order to account for more complex relationships between alcohol consumption and disease/injury onset. Except for injuries and single disease groups, which require separate approaches (see e.g. (Rehm, Probst, Shield, & Shuper, 2017; Ye et al., 2019)), AAF are calculated with the following equations:

**Equation 1.2:**

$$AAF = \frac{P_{FD}\,(RR_{FD}-1) + \int_{>0}^{150} P_{CD}(x)(RR_{CD}(x)-1)dx}{1 + P_{FD}\,(RR_{FD}-1) + \int_{>0}^{150} P_{CD}(x)(RR_{CD}(x)-1)dx}$$

**Equation 1.3:**

$$AAF = \frac{P_{FD}\,(RR_{FD}-1) + P_{CD}(RR_{CD}-1)}{P_{FD}\,(RR_{FD}-1) + P_{CD}(RR_{CD}-1) + 1}$$

$$P_{CD}(RR_{CD}-1) = \int_{>0}^{60} P_{CDNB}(x)RR_{CDNB}(x)dx + \int_{>0}^{60} P_{CDB}(x)RR_{CDB}(x)dx + \int_{>60}^{150} P_{CDB}(x)RR_{CDB}(x)dx \; - P_{CD}$$

As with the classic PAF ***Equation 1.1***, both AAF formulae, ***Equation 1.2*** and ***Equation 1.3***, combine information about the prevalence of exposure (here former ($P_{FD}$) and current drinkers ($P_{CD}$)) with the respective risk function ($RR_{FD}$ and $RR_{CD}$). ***Equation 1.3*** is used only for diseases that are impacted by irregular heavy drinking occasions (e.g. ischemic heart diseases). The key difference to ***Equation 1.2*** is that for current drinkers with less than 60 gram of pure daily alcohol intake, there are two separate risk functions – one for those who *do not* drink heavily on single occasions ($P_{CDNB}(x)RR_{CDNB}(x)dx$) and one for those who *do* drink heavily on single occasions ($P_{CDB}(x)RR_{CDB}(x)dx$). Overall, these formulae can be considered extensions of the classic PAF formula from Levin (***Equation 1.1***). The main difference is that the AAF formulae allow to model variations of disease risk with different drinking levels and patterns, rather than assuming that the risk remains the same for all drinkers, regardless of their drinking levels.

Thus, to calculate AAF we require information on 1) key alcohol exposure indicators and 2) the link between alcohol consumption and disease onset. These data will be described in detail below.

1) Key alcohol exposure indicators

Alcohol exposure indicators comprise the prevalence of former drinkers (those who drank in their life but not in the past year, $P_{FD}$ in ***Equation 1.2*** and ***1.3***) and current drinkers (those who drank in the past year, $P_{CD}$ in ***Equation 1.2*** and ***1.3***). Among current drinkers, two more parameters are required: First, the group of current drinkers need to be distributed alongside a continuum of average drinking levels, which is measured in grams of pure alcohol consumed per day. This distribution can be derived from APC using a gamma distribution, which allows to estimate the prevalence of drinkers at each given drinking level in the population (Kehoe, Gmel, Shield, Gmel, & Rehm, 2012). Second – and this is only relevant for diseases which are impacted by drinking patterns – current drinkers need to be split into those who do drink heavily on irregular occasions and those who do not. This indicator is commonly defined as at least one occasion in the past 30 days on which at least 60 grams of pure ethanol was consumed (equivalent to three large bottles of beer) (World Health Organization, 2018b).

2) Link between alcohol consumption and disease onset

The link of between alcohol consumption and disease onset is also termed as risk function, which denotes the relative risk (RR) at a given drinking level. For some diseases and injuries, however, average drinking levels are insufficient to describe the risk as consumption of larger amounts of alcohol on single occasions increase the risk over and above average drinking levels (e.g. for ischemic heart diseases, see (Bagnardi, Zatonski, Scotti, La Vecchia, & Corrao, 2008; Roerecke & Rehm, 2010)). As a result of these considerations, disease-specific dose-response relationships between average drinking levels and risk of disease onset need to be established, in addition to the impact of irregular heavy drinking occasions, if applicable. For illustration purposes, the dose-response relationship for ischemic heart diseases is presented in ***Figure 1.2*** as estimated from meta-analyses (taken from Appendix of (Rehm, Gmel, et al., 2017) and based on (Rehm, Shield, Roerecke, & Gmel, 2016)).

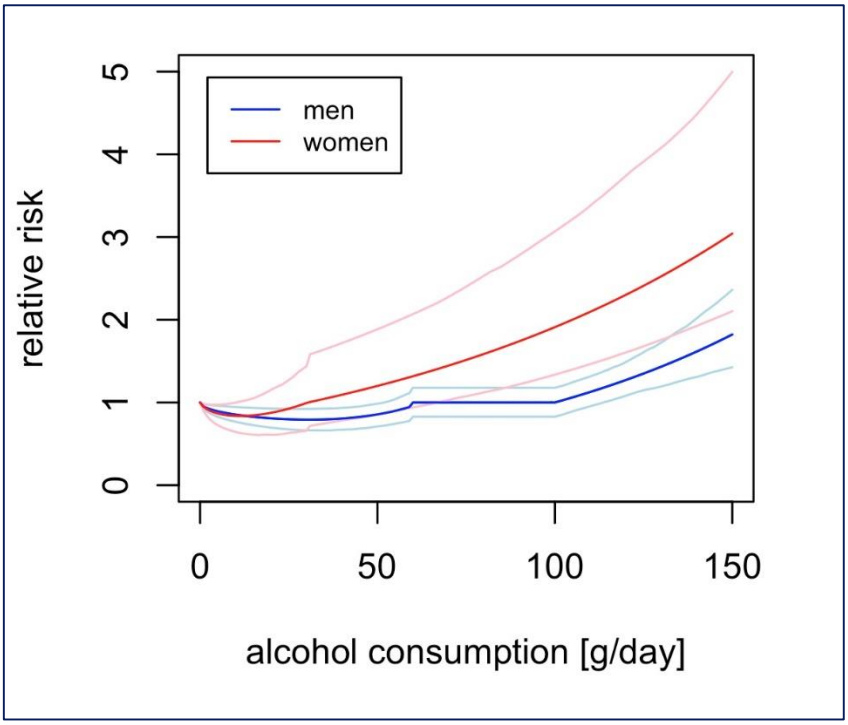


**Figure 1.2** Sex-specific dose-response relationship between average drinking levels and relative risk of ischemic heart disease for people aged 35 to 64 (taken from (Rehm, Gmel, et al., 2017))

Ischemic heart diseases will be used as example to show that calculation of AAF is not a trivial exercise and depends on a number of parameters. As illustrated in **Figure 1.2**, the risk function does not increase monotonously with drinking levels, but instead follows a so-called J-curve. In other words, alcohol consumption has a protective effect for ischemic heart disease at lower drinking levels and a detrimental effect at higher drinking levels. Further, for drinkers with irregular heavy drinking patterns, the shape of this risk curve would look different as the protective effect for low drinking levels can disappear or even turn into a detrimental effect, if alcohol is consumed in larger doses on single occasions (Rehm et al., 2016; Roerecke & Rehm, 2010).

In summary, the alcohol-attributable disease burden can be determined using AAF, which are estimated by combining population alcohol exposure and disease-specific risk functions. In fact, a consistent set of all relevant population alcohol exposure figures has been estimated for all countries (Manthey et al., 2019). However, risk functions could not be established for all diseases for which alcohol has been identified to be a contributory cause. This concerns rather infrequent diseases, such as esophageal varices (ICD-10: I85), selected neoplasms (e.g. neoplasm of small intestine, ICD-10: C17), and ACM (ICD-10: I42.6).

For ACM, a 2017 published review of the relationship between alcohol consumption and cardiomyopathy (CM) concluded, that a meta-analysis on risk functions could not be performed given the lack of comparable and systematic data (Rehm, Hasan, Imtiaz, & Neufeld, 2017). However, without a risk function that can be generalized across populations, the alcohol-attributable burden from CM cannot be assessed, which results in the overall alcohol-attributable disease burden to be an underestimate. Thus, in order to include ACM in estimates of the alcohol-attributable disease burden, an alternative approach to the methodology is required.

## 1.4 Cardiomyopathy

Before summarizing the link between alcohol consumption and CM in the next section, CM as a prominent CVD is briefly described.

According to the ICD-10, CM refers to a heterogeneous group of CVD, which can be classified based on pathophysiological features (dilated CM; hypertrophic CM; restrictive CM) or etiological factors (e.g. ACM) (World Health Organization, 1993). The American Heart Association proposed to classify CM into primary and secondary CM, with the former being largely confined to the heart muscle (Maron et al., 2006). In secondary CM, however, the myocardium is only one out of multiple organs affected, with large variations of myocardial involvement. Among primary CM, the two most common types are hypertrophic and dilated CM (Brieler, Breeden, & Tucker, 2017).

Hypertrophic CM is a autosomal dominant genetic heart disease, which is characterized by a non-dilated, hypertrophied (i.e. increased) left ventricle (Maron et al., 2006). Mutations in at least eleven genes have been linked to hypertrophic CM (Maron & Maron, 2013) and genetic screenings suggest prevalence estimates between 0.2% and 0.5% of the general population (Maron et al., 1995; Semsarian, Ingles, Maron, & Maron, 2015) among all ages (Maron & Maron, 2013). If diagnosed, the prognosis for people with hypertrophic CM is largely favorable and not associated with substantial reductions of life expectancy (Adamczak & Oko-Sarnowska, 2018; Maron, Casey, Hauser, & Aeppli, 2003). However, hypertrophic CM has also been identified as major cause for sudden cardiac deaths, e.g. among athletes (Finocchiaro, Papadakis, Sharma, & Sheppard, 2017; Maron, Doerer, Haas, Tierney, & Mueller, 2009), which warrants the need to identify hypertrophic CM through routine screening.

Dilated CM, on the other hand, is characterized by a dilated left ventricle and systolic dysfunction and is the leading indication for heart transplantation globally (Brieler et al., 2017; Weintraub, Semsarian, & Macdonald, 2017). As compared to hypertrophic CM, dilated CM occurs mainly among 40 to 59 year old people (Brieler et al., 2017) and is less prevalent overall, with about one in 2,500 persons (0.04%) being affected (Maron et al., 2006). The survival rates for dilated CM were estimated at 50% within five years and one in eight patients die a sudden death (Weintraub et al., 2017). Dilated CM is caused by genetic and non-genetic factors, while around 20% to 35% of cases are estimated to be transmitted genetically (Grünig et al., 1998; Michels et al., 1992; Weintraub et al., 2017). For the remaining cases, a range of causes have been determined, which include myocardial infection (myocarditis), autoimmune diseases, nutritional deficiency, endocrinological factors, as well as drug and alcohol use (Maron et al., 2006; Weintraub et al., 2017).

Other ways to classify CM do exist, listing ischemic CM a prominent type. However, as ischemic CM is merely reflecting consequences of other cardiovascular diseases, such as myocardial ischemia and infarction, this term was voted to be excluded from the classification system proposed by the American Health Association in 2006 (Brieler et al., 2017; Maron et al., 2006).

## 1.5 Alcohol and cardiomyopathy

The association between alcohol consumption and CM has first been described in 1884, when Prof. Bollinger identified 'a plethora of beer enjoyment' as the reason for distinctively high rates of cardiac hypertrophy and dilation in Munich, Germany (Bollinger, 1884). At that time, annual per capita consumption of beer in Munich was reported at 432 liters (~22 liters pure alcohol) as compared to 88 liters in the entire customs jurisdiction of Germany. According to the report, an enlarged heart muscle has been determined as main cause of death in 46 out of 1,000 autopsies.

In his presentation, Bollinger indicated that alcohol consumption was not acknowledged as risk factor for enlargement of the myocardium by the majority of his colleagues. Today, this link is widely recognized with a separate disease code, marked as ACM, existing ever since the ninth revision of the ICD series (World Health Organization, 1978). With regard to the classification of primary and secondary CM (see **1.4**), ACM does not fall into one of these categories unambiguously (Piano, 2002). As the pathophysiology of ACM resembles that of dilated CM, it is sometimes regarded a special case of dilated CM and thus classified as primary CM (see e.g. (Maron et al., 2006)). However, ACM is sometimes also classified as secondary CM together with other toxic agents or diseases that affect the myocardium among other organs (see e.g. (Weintraub et al., 2017)).

The key features of ACM are dilation of the left ventricle and accordingly a contractile dysfunction, which manifests in comparably high end-diastolic volume, increased mass and reduced wall thickness of the left ventricle, and a decreased ejection fraction (Maisch, 2016; Piano & Phillips, 2014). All of these characteristics, however, are not specific to ACM but are common to all dilated CM and can thus be caused by other factors as well (Weintraub et al., 2017).

How does alcohol consumption cause damages to the myocardium? In an early experimental landmark study, heavy alcohol consumption has been found to reduce cardiac contractility as measured in high end-diastolic pressure (Regan et al., 1969) - this has been corroborated by subsequent studies (for a review of experimental studies, see (Guzzo-Merello, Cobo-Marcos, Gallego-Delgado, & Garcia-Pavia, 2014)). In order to understand the underlying process of cardiac changes caused by heavy alcohol consumption, the effects of ethanol on cell structures have been extensively studied in recent decades. Two systematic reviews on the mechanism of alcohol-induced myocardial alterations agreed that chronic heavy alcohol consumption can cause adverse intracellular effects and cell death (apoptosis), as well as impaired synthesis of myocardial proteins (Guzzo-Merello et al., 2014; Piano & Phillips, 2014). Alcohol-induced oxidative stress, changes in mitochondrial functions, and the impact on long-chain fatty acid uptake have been described as important key mechanisms for cardiac changes and ultimately reductions in cardiac output. In fact, alcohol-induced cell death is not limited to the myocardium but has also been observed in nerve cells, which explains development of fetal alcohol syndrome (Farber & Olney, 2003). Lastly, it should also be noted that some of the outlined alcohol-induced cardiotoxic effects are genetically mediated (Duan et al., 2002; Ware et al., 2018).

In summary, there is a solid body of biologically plausible evidence for the link between chronic heavy alcohol consumption and incidence of CM, with recent studies pointing out the substantial role of genetic susceptibility. However, studies remained inconclusive on the link of alcohol intake levels and pathogenesis of ACM – the key requirement for determining risk functions for ACM.

In their review, Rehm and colleagues aimed to quantify the dose-response relationship between alcohol intake levels and ACM incidence (Rehm, Hasan, et al., 2017). They identified several case-control studies linking chronic high levels of alcohol exposure (at least 60 to 80 grams of pure alcohol per day) to dilated CM (Gillet et al., 1992; Komajda et al., 1986; McKenna, Codd, McCann, & Sugrue, 1998). While this link was further corroborated by population (Manolio, Levy, Garrison, Castelli, & Kannel, 1991) and clinical studies (Joaquim Fernández-Solà et al., 2000; Lazarević et al., 2000), there are too few epidemiological studies to derive a generalizable risk function for ACM.

# 2 Aims and objectives

At the start of the dissertation project, alcohol-attributable burden of disease estimates excluded ACM as methods to quantify the contribution from alcohol to CM were lacking. Thus, the main aim is 1) to develop methods for estimating the contribution of alcohol consumption to CM using data from countries with civil registries and 2) to apply these methods to obtain global estimates of the mortality attributable to ACM.

While pursuing these aims, another method to estimate ACM mortality has been proposed by the Institute for Health Metrics and Evaluation. In response, differences in results and underlying assumptions of both approaches in estimating ACM mortality were assessed, which represents aim 3) of this dissertation.

# 3 Study design and methodology

## 3.1 Study design

The dissertation was split into three distinct studies – in alignment with the three study aims - and for each, cross-sectional analyses of civil registry mortality data were undertaken to 1) develop and 2) apply methods for estimating alcohol-attributable mortality of ACM and to 3) critically assess validity of an alternative method.

As outlined in ***section 1.3***, the usual methods in estimating the contribution of alcohol to a given disease involves a comparative risk assessment, resulting in calculation of AAF (Murray et al., 1996; World Health Organization, 2018b). However, a core prerequisite to apply these methods for ACM is the establishment of a risk function, which was not possible due to the lack of epidemiological studies (Rehm, Hasan, et al., 2017). As an alternative approach to calculate AAF, using the proportion of the number deaths from ACM relative to the number of deaths from any CM, as expressed in ***Equation 3.1***, is proposed:

**Equation 3.1:**

$$AAF_{any\ cardiomyopathy} = \frac{Mortality_{ACM}}{Mortality_{Any\ cardiomyopathy}}$$

In order to estimate AAF for CM, readily available mortality data from civil registries from nearly 100 countries were used. The calculation was performed at country level and by sex. For countries where civil registry data was not available, estimating AAF using regression analyses while considering the relationship of the underlying cause of ACM, population alcohol exposure, and mortality from any CM is proposed.

## 3.2 Data sources

### 3.2.1 Mortality data

As primary source of information for the entire dissertation served the publicly available WHO mortality database, providing civil registry data from more than half of all member WHO states (World Health Organization, 2018c). In accordance with the ICD-10, deaths need to be assigned recognized cause of death codes in order to be included in the WHO mortality database (World Health Organization, 2019c). Of note, the underlying cause of death code is defined as "the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury" (World Health Organization, 1993). Conversely, countries not adhering to the ICD-10 in coding mortality or countries without civil registry system covering the entire country are not represented in the WHO mortality database. Given the rich and reliable compilation of mortality data for a large number of countries spanning across decades, the WHO mortality database has become a core source of information in various areas of global health research and monitoring, for instance for the GBD study (Roth et al., 2018) or for global cancer monitoring (International Agency for Research on Cancer, 2019).

Two additional sources of mortality data were used in the dissertation: the WHO Global Health Estimates (World Health Organization, 2017a) and the GBD Results Tool (Institute for Health Metrics and Evaluation, 2019). In contrast to the WHO mortality database reporting vital registry data, these two databases provide mortality *estimates*, which are complete and consistent for all countries and aggregated into larger disease groups (e.g. all ischemic heart disease codes I20-I25 grouped together). Both of these databases largely overlap in defining disease groups, but some differences have been identified for select countries and disease groups (Shield et al., 2020).

Mortality data from these three databases (WHO mortality database, WHO Global Health Estimates, GBD Results Tool) have laid the foundation for the analyses across all three studies and are summarized in **Table 3.1**.

**Table 3.1** Extraction of mortality data from different sources in different studies

| | **WHO Mortality database** | **WHO Global Health Estimates** | **GBD Results Tool** |
|---|---|---|---|
| Study I | ACM; any cardiomyopathy* | / | ACM |
| Study II | ACM | any cardiomyopathy* | / |
| Study III | ACM; any cardiomyopathy*; any cardiovascular diseases; selected garbage codes | / | ACM; any cardiomyopathy*; any cardiovascular diseases |

Note: any cardiomyopathy was defined differently in each of the studies. See respective section for details.

### 3.2.2 Covariate data

The primary aim of this dissertation was to estimate AAF for all countries using regression analyses. As outlined in ***section 1.5***, chronic heavy drinking over a sustained period has been identified as necessary precursor to ACM. While minimum thresholds in terms of volume and length of sustained drinking have not be established to date, there are three indicators available at the population level, which were expected to be highly correlated with chronic heavy drinking patterns:

1) APC (in Liters per adult per year)
2) Prevalence of heavy episodic drinking (HED), defined as the proportion of adults reporting at least one intake of at least 60 grams pure alcohol in the past 30 days
3) Prevalence of AUD, defined as the proportion of adults meeting ICD-10 criteria of AUD in the past 12 months

APC has been acknowledged as the most reliable estimate for alcohol consumption in a given country (Poznyak et al., 2013) and can be derived from combining recorded consumption from official statistics (e.g. taxation) with estimates on unrecorded consumption, corrected for tourist consumption (for more details, see (World Health Organization, 2018b)). Per definition, APC is calculated for the entire population – including those abstaining from drinking alcohol. Adjusting APC with the prevalence of current drinkers results in a more realistic indicator of population alcohol exposure. On the other hand, prevalence of HED and AUD may be a closer approximation to drinking patterns causally related to ACM, however respective estimates are survey-based and subject to reporting errors (Del Boca & Darkes, 2003), sampling bias (Shield & Rehm, 2012), and cultural differences (Rehm & Room, 2015). All three indicators have been sourced from the Global Information System on Alcohol and Health (World Health Organization, 2018a) or the Global Status Report on Alcohol and Health from 2014 (World Health Organization, 2014) and have been considered for inclusion in regression analyses in study I (see ***section 4****)* and partially included in study II (see ***section 5****)* and study III (see ***section 6****)*.

In addition to alcohol-specific variables, data on population size and economic wealth indicators were processed at different steps in this project, as well. First, country-specific population size is crucial for standardizing mortality counts (e.g. by calculating mortality rates) and has been sourced from official United Nation statistics (Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, 2017). Second, given the close link between health and wealth (Cole, 2019), an indicator of economic wealth has been considered for inclusion in regression models. In this dissertation, economic wealth was operationalized as GDP at Purchasing Power Parity (PPP) and was retrieved from the World Bank (World Bank, 2017).

# 4 Study I - Quantifying the global contribution of alcohol consumption to cardiomyopathy


## Abstract

**Background** The global impact of alcohol consumption on deaths due to CM has not been quantified to date, even though CM contains a subcategory for ACM with an effect of heavy drinking over time as the postulated underlying causal mechanism. In this feasibility study, a model to estimate the AAF of CM deaths based on alcohol exposure measures is proposed. **Methods** A two-step model was developed based on aggregate-level data from 95 countries, including the most populous (data from 2013 or last available year). First, the crude mortality rate of ACM per 1,000,000 adults was predicted using a negative binomial regression based on prevalence of AUD and APC (*N*=52 countries). Second, the proportion of ACM among all CM deaths (i.e., AAF) was predicted using a fractional response probit regression with ACM crude mortality rate (from Step 1), AUD prevalence, APC per drinker, and GBD region as predictions. Additional models repeated these steps by sex and for the wider GBD study definition of CM. **Results** There were strong correlations (> 0.9) between the crude mortality rate of ACM and the AAF, supporting the modeling strategy. In the first step, the population-weighted mean crude mortality rate was estimated at 8.4 ACM deaths per 1,000,000 (95% CI: 7.4–9.3). In the second step, the global AAF were estimated at 6.9% (95% CI: 5.4–8.4%). Sex-specific figures suggested a lower AAF among females (2.9%, 95% CI: 2.3–3.4%) as compared to males (8.9%, 95% CI: 7.0–10.7%). Larger deviations between observed and predicted AAF were found in Eastern Europe and Central Asia. **Conclusions** The model proposed promises to fill the gap to include AAF for CM into comparative risk assessments in the future. These predictions likely will be underestimates because of the stigma involved in all fully alcohol-attributable conditions and subsequent problems in coding of ACM deaths.

## 4.1 Background

Alcohol consumption is a major risk factor for the global burden of disease (GBD 2015 Risk Factors Collaborators, 2016; Rehm et al., 2009; World Health Organization, 2014). It has causal relationships with more than 200, three-digit ICD-10 (World Health Organization, 1993) disease and injury categories (Rehm et al., 2009). Two related dimensions of alcohol consumption have been shown to impact disease and injury: (average) level of alcohol consumption and heavy drinking occasions (Rehm, Baliunas, et al., 2010; Rehm, Gmel, et al., 2017; Rehm et al., 2003). Among the causally related disease and injury categories, there are about 40 that are fully (i.e., 100%) alcohol-attributable, such as AUD (for a list of all fully alcohol-attributable disease and injury categories see (Rehm, Baliunas, et al., 2010)). However, many of the fully alcohol-attributable disease and injury categories have not been included in the GBD estimates to date, as there are no global data for smaller causes of death (Rehm & Imtiaz, 2016), given the unavailability of vital registries for the majority of the global population (Mikkelsen et al., 2015).

To date, the contribution of alcohol to CM has not been quantified globally. CM (ICD-10 I42) denotes a disease of the heart muscle, reducing its ability to pump blood to the rest of the body. There are multiple forms of CM with different etiologies, but chronic, heavy alcohol consumption is associated with dilated CM, as ethanol acts as a toxin to weaken the heart muscle (Dancy, Bland, Leech, Gaitonde, & Maxwell, 1985; J. Fernández-Solà, 2015; Rubin, 1979; Sander, von Heymann, Spies, & Braun, 2005; Alvaro Urbano-Marquez et al., 1989; A. Urbano-Marquez & Fernandez-Sola, 2004). There is sufficient evidence for causality, based on experimental evidence of the toxic effect of alcohol on muscles and cardiac indicators (Kozlovskij, 2007; Song & Rubin, 1972); and there is even a category of ACM in ICD-10 (I42.6) (World Health Organization, 1993). ACM has been known since the mid-19$^{th}$ century (e.g., (Wood, 1855); for an overview of historical accounts see (Massumi et al., 1965)), as detailed by a Munich pathologist, who labeled the phenomenon the “Münchner Bierherz” (the Munich beer heart), a disease characterized by cardiac dilatation and hypertrophy due to heavy consumption of beer over time (Bollinger, 1884). However, for the reasons indicated above, the category of ACM is not part of global statistics.

To quantify the relationship between alcohol consumption and CM for future comparative risk assessments, the usual procedure would be to conduct a meta-analysis on the dose-response relationship between level of alcohol consumption and risk of CM, as has been done for all the other disease and injury categories partially attributable to alcohol (Rehm, Baliunas, et al., 2010; Rehm, Gmel, et al., 2017). In addition, as cardiovascular outcomes are often impacted by patterns of drinking (e.g., (Roerecke & Rehm, 2014)), the potential impact of this dimension would be estimated as well. While a recent systematic review did not find enough empirical studies to quantify either relationship (Rehm, Hasan, et al., 2017), results from the identified studies suggested a threshold relationship between alcohol use and CM with a potential dose-response relationship for different levels of heavy consumption. With regard to specific drinking characteristics, heavy drinking (defined as > 80g pure alcohol/day) over a decade or more (Gillet et al., 1992) was repeatedly found as key risk factor for developing CM (see also (Guzzo-Merello et al., 2014; Piano, 2002; Rehm, Hasan, et al., 2017)). Based on these findings, predicting ACM and/or modeling the relationship between ACM and CM using aggregate alcohol and mortality data was expected to be feasible.

While a population measure of alcohol consumption such as the rate of consuming more than 80g pure alcohol on average per day over time would be best used to model ACM, this indicator is not available globally. Instead, prevalence of AUD and HED, as well as APC can be considered potential substitute measures to predict the AAF for CM. In fact, APC is closely linked to heavy drinking, as the distribution of drinking follows a gamma distribution and its mean determines the spread (in a one-parameter distribution). Thus, APC directly corresponds to the proportion of heavy drinkers (Kehoe et al., 2012; Rehm, Kehoe, et al., 2010).

Predictions for both CM and the larger category of CM in the GBD study (Global Burden of Disease Study 2015, 2016) were performed in this feasibility study. However, CM is responsible for 84% of deaths in the larger GBD category of CM based on the countries included in the present study, and thus the AAF were not expected to differ widely.

## 4.2 Methods

We followed the Guidelines for Accurate and Transparent Health Estimates Reporting in the presentation of the global health estimates (Stevens et al., 2016) (detailed checklist can be found in the **Appendix A (study I)** - Additional file A.1).

### 4.2.1 Data sources

We sought to establish a model for estimating AAF for CM based on data from 48 of the 50 most populous countries (exceptions: Sudan and Myanmar), as well as from all countries of the WHO European Region and select countries from other WHO regions (total of 95 countries included). The selection of countries was guided by three considerations: 1) we wanted to ensure that the methodology could be used for global estimates, where 48 of the 50 most populous countries included 86% of the global population in 2015; 2) we wanted to include Eastern European countries, where AAF for CM can be high (e.g., 67% found in a city of Russia (Leon, Shkolnikov, McKee, Kyrianov, & Andreev, 2011); see also Table 3 below); and 3) we wanted to ensure global spread. Altogether the selected countries represented 91% of the global population 15 years and older in 2015.

Alcohol exposure data (HED, AUD, APC) were taken from the Global Information System on Alcohol and Health of WHO (World Health Organization, 2016a); for the percentage of pure alcohol consumed by men and women, we relied on data from the Global Status Report on Alcohol and Health (World Health Organization, 2014). Mortality data from 2013 (or last available year) were taken from the WHO Mortality Database (World Health Organization, 2015), with the exception of Russia (Rosstat, 2015), Slovenia (B. Lovrečič & Lovrečič, 2016), and Ukraine [personal communication of Dr. Andriy Samokhvalov]. Additionally, we used United Nations data for population size (United Nations, 2013), as well as World Bank GDP Purchasing Power Parity (PPP) corrected per capita data for measuring comparative wealth of countries (The World Bank, 2016). Countries were classified into GBD regions, as per the methodology of the Institute for Health Metrics and Evaluation (Institute for Health Metrics and Evaluation, 2016). All data were matched to year of mortality data (63.3% = 2013) for each country and referred to the adult population (15 years or older). All data were obtained from publicly available international databases that have been previously used in the modeling of Global Health Estimates (World Health Organization, 2017a) or within the GBD studies (e.g., (GBD 2015 Mortality and Causes of Death Collaborators, 2016)). We did not expect any systematic bias in the data used for this study, except for the underestimation of ACM because of stigma and coding problems (discussed in detail below).

### 4.2.2 Modeling strategy

The AAF for CM were modeled in a two-step procedure using aggregate data from 95 countries. In this procedure, we modeled the crude mortality rate for ACM per year (i.e., number of ACM deaths per 1,000,000 adults per year, where adults were defined as 15 years and older to correspond to the APC definition), which was subsequently used in the second step to predict the proportion of ACM deaths among all CM deaths (i.e., the AAF). The rationale for this two-step procedure was based on high correlations between crude mortality rate and the AAF. Results from Spearman correlations between these right-skewed variables (*N*=49; ρ=0.93, 95% CI: 0.88–0.96; for women: ρ=0.98, 95% CI: 0.97–0.99; for men: ρ=0.93, 95% CI: 0.88–0.96) supported the reasoning of this two-step strategy.

Prior to model building, bivariate Spearman correlations between potential predictors and both outcomes were examined (see results in **Table 4.1**; see scatterplots in **Figure A.1**, **Figure A.2**, **Figure A.3** and **Figure A.4**). Correlations between the predictors and with crude mortality rate ranged between ρ=0.36 and ρ=0.69. Further, large correlations were observed between APC total, prevalence of AUD, and HED ($0.71 < \rho < 0.76$).

**Table 4.1** Spearman correlation matrix of alcoholic cardiomyopathy crude mortality rate, alcohol-attributable fraction of cardiomyopathy deaths, and potential predictors

| | **APC total** | **APC among drinkers** | **AUD prevalence** | **HED prevalence** | **ACM crude mortality rate** | **AAF of CM deaths** |
|---|---|---|---|---|---|---|
| APC total | 1 | / | / | / | / | / |
| APC among drinkers | 0.36 | 1 | / | / | / | / |
| AUD prevalence | 0.71 | 0.09 | 1 | / | / | / |
| HED prevalence | 0.76 | 0.00 | 0.74 | 1 | / | / |
| ACM crude mortality rate | 0.69 | 0.49 | 0.41 | 0.40 | 1 | / |
| AAF of CM deaths | 0.52 | 0.37 | 0.38 | 0.36 | 0.93 | 1 |

Note: APC = Alcohol per capita. AUD = Alcohol Use Disorder. HED = Heavy Episodic Drinking. ACM = Alcoholic Cardiomyopathy. AAF = Alcohol-attributable fractions. CM = Cardiomyopathy. Bivariate correlations based on all available data for each pair.

In the first step, the country-specific ACM crude mortality rate was modeled using negative binomial regression. The prediction initially included prevalence of AUD and HED, as well as total APC. However, HED was removed from the final model (see ***Equation 4.1*** below), as it did not improve its predictive accuracy over the simpler model (see below for a description of assessment of goodness of fit; difference in Pseudo-$R^2$=0.002; likelihood ratio test: $Chi^2(1)$=0.55, *p*=0.46). The results of the first-step model were integrated into one variable combining the predicted (*N*=43 countries) and observed (*N*=52 countries) crude mortality rates for ACM. In the second step, the AAF were predicted using the crude mortality rate for ACM from Step 1, as well as prevalence of AUD and HED, APC per drinker, and GBD region using a fractional response probit regression (Papke & Wooldridge, 1996). As in the first-step model, we excluded HED from the final model (see ***Equation 4.2*** below) because accuracy of predictions could not be improved by retaining it (difference in Pseudo-$R^2$=0.002; likelihood ratio test not meaningful for robust standard error models). We additionally tested the contribution of economic wealth by the inclusion of GDP PPP into the model, but it did not improve the accuracy of the prediction.

**Equation 4.1**: negative binomial regression written as generalized linear model

$$\text{ACM crude mortality rate} = f(\beta_0 + \beta_1 * \ AUD\ prevalence + \beta_2 * APC\ total)$$

*Link function*: log

*Distribution*: negative binomial

*Variance*: $Var[Y|x] = \ \mu + \alpha\mu^2$

**Equation 4.2**: fractional response probit regression written as generalized linear model

$$\text{P(AAF=1)} = f(\beta_0 + \ \beta_1 * crude\ mortality\ rate + \beta_2 * AUD\ prevalence + \beta_3 * APC\ drinker + \beta_4 * GBD\ region)$$

*Link function*: probit

*Distribution*: binomial

In addition to this model (Model 1), the same analyses were performed separately by sex (Model 2), as there is evidence for a higher risk of ACM for women compared to men given the same level of drinking (for sex differences see (Urbano-Márquez et al., 1995) and (J. Fernández-Solà et al., 1997)). However, sex-specific ACM crude mortality rates could not be obtained for Ukraine, reducing the available observations for these rates in the first step to 51 countries. In two further models (Models 3 and 4), the second step was repeated with the same predictors for the AAF using the broader GBD definition of CM. However, some of the ICD-10 categories that were part of the broader GDB definition of CM were not included, as they were not available from the WHO Mortality Database. Similar to the first two models, this was performed for the entire population (Model 3) and separately by sex (Model 4).

To assess the goodness of fit for all models, we used the pseudo $R^2$ methods (likelihood ratio of the full model compared to the null model) (McFadden, 1973). In addition, we compared predicted and observed indicators for both steps. An absolute difference of at least 10 deaths per 1,000,000 (Step 1) and of 5% in the proportion of ACM deaths among all CM deaths (Step 2) were considered relevant deviations. Systematic differences in GDP PPP (using t-test), AUD prevalence (using t-test), and in the regional distributions (using standardized deviations larger than 1.96) were identified and described between countries within and beyond these thresholds.

In order to generalize the estimates, outcomes from both steps (crude mortality rate and AAF), were weighted by the population size of the given country. The weighted variance was obtained using the standard formula for sums of weighted variances (see ***Equation 4.3*** below), assuming that the covariance between countries was zero. Variances were then used to estimate standard error and 95% CI. Altogether, the rates (Step 1) and proportions (Step 2) were presented in three ways: 1) unweighted predicted rates/proportions; 2) predicted rates/proportions weighted for population size; and 3) observed and predicted (including observed values first and if missing – predicted values) rates/proportions weighted for population size.

**Equation 4.3**: Estimation of population weighted variance

$$\mathrm{Var}\left(\sum_{i}^{n} a_i X_i\right) = \sum_{i=1}^{n} a_i^2\, Var(X_i) + 2\sum_{1\le i}\sum_{<j\le n} a_i a_j Cov(X_i, X_j)$$

Analyses were performed using Stata 14.0 (Stata Corporation, 2015) and R (R Core Team, 2016). The file and the corresponding syntax for all calculations can be found in **Appendix A (study I)** (Additional file A.2 and A.3).

## 4.3 Results

A two-step model predicted (1) the ACM crude mortality rate and (2) the AAF for CM deaths in 95 selected countries.

### 4.3.1 Step 1: Crude mortality rate of alcoholic cardiomyopathy

In Model 1 - Step 1, the ACM crude mortality rate was predicted based on 52 countries using a negative binomial regression (see ***Equation 4.1***). In **Table 4.2**, both observed (*N*=52) and predicted (*N*=95) crude mortality rates are presented, while all model parameters (intercept, coefficient, dispersion parameter, Pseudo $R^2$) can be found in the **Appendix A (study I)** (Additional file A.4; Sheet "Model 1 (total)"). The predicted rates ranged between 0.7 (Saudi Arabia) and 267.9 (Belarus) ACM deaths per 1,000,000. Comparing the observed and predicted rates, the mean absolute difference amounted to 16.8 ACM deaths per 1,000,000 (min: 0.4, max: 150.2, median: 7.3), with 37 countries (71.2%; representing 81.8% of the entire population with observed ACM mortality data) within a range of +/- 10 ACM deaths per 1,000,000 adults (countries beyond the threshold are highlighted in **Table 4.2**). Comparing countries within and beyond this threshold, we found that countries with large deviations between observed and predicted ACM crude mortality rates had a similar GDP PPP ($30,542 versus $35,820, t-test: *p*=0.382) but higher AUD prevalence (4.9% versus 9.0%, t-test: *p*=<0.001). With respect to deviations by region, higher deviations were more common in Eastern European countries (one country within threshold versus five countries beyond threshold; standardized deviation = 3.13). Excluding Eastern European countries, the mean absolute difference between observed and predicted crude mortality rates fell from 16.8 to 11.5 cases per 1,000,000 (min: 0.4, max: 149, median: 5.6).

For the included countries, an unweighted average of 15.2 ACM deaths per 1,000,000 was predicted (95% CI: 9.2–21.2). The weighted ACM crude mortality rate based on predicted values only was estimated to be 11.4 per 1,000,000 (95% CI: 10.1–12.6), whereas the mean weighted ACM crude mortality rate combining both observed and predicted values was estimated to be 8.4 ACM deaths per 1,000,000 (95% CI: 7.4–9.3). The results of sex-specific predictions (Model 2, Step 1) can be found in **Appendix A (study I)** (Additional file A.4; Sheets "Model 2 (female)" and "Model 2 (male)"). The weighted average ACM mortality rate of observed and predicted deaths was estimated to be 2.8 (95% CI: 2.4–3.3) and 12.9 (95% CI: 11.3–14.6) deaths per 1,000,000 for females and males, respectively. Both the observed and predicted crude mortality rates in males were greater than or equal to those of females in all included countries.

**Table 4.2** Observed and predicted alcoholic cardiomyopathy deaths per 1,000,000 people, by country

| Country | ACM crude mortality rate | | 95% Confidence interval | |
|---|---|---|---|---|
| | Observed | Predicted | Lower bound | Upper bound |
| Afghanistan | | 0.77 | 0.21 | 2.76 |
| Albania | | 5.00 | 2.81 | 8.88 |
| Algeria | | 0.98 | 0.30 | 3.16 |
| Argentina | 0.22 | 8.60 | 5.56 | 13.32 |
| Armenia | | 4.27 | 2.16 | 8.45 |
| Australia | 2.08 | 7.40 | 3.50 | 15.62 |
| Austria | 1.93 | 26.44 | 13.58 | 51.50 |
| Azerbaijan | | 2.48 | 0.86 | 7.16 |
| Bahrain | | 1.08 | 0.35 | 3.35 |
| Bangladesh | | 0.81 | 0.23 | 2.89 |
| Belarus | | 267.94 | 44.31 | 1620.15 |
| Belgium | 2.50 | 9.87 | 6.36 | 15.32 |
| Bosnia and Herzegovina | | 5.37 | 3.13 | 9.22 |
| Brazil | 1.61 | 7.29 | 4.62 | 11.49 |
| Bulgaria | | 15.65 | 9.65 | 25.36 |
| Canada | 1.70 | 11.45 | 7.35 | 17.83 |
| Chile | 1.22 | 6.76 | 4.22 | 10.81 |
| China | | 5.10 | 2.97 | 8.76 |
| Colombia | 0.00 | 4.77 | 2.34 | 9.75 |
| Costa Rica | 1.38 | 4.15 | 1.88 | 9.18 |
| Croatia | 11.31 | 14.32 | 6.79 | 30.21 |
| Cyprus | 0.00 | 11.10 | 6.94 | 17.77 |
| Czech Republic | 2.56 | 12.14 | 5.97 | 24.71 |
| Democratic People's Republic of Korea | | 2.08 | 0.88 | 4.94 |
| Democratic Republic of the Congo | | 2.41 | 0.99 | 5.86 |
| Denmark | 3.25 | 8.71 | 5.58 | 13.59 |
| Egypt | | 0.72 | 0.19 | 2.68 |
| Estonia | 70.57 | 39.44 | 17.50 | 88.89 |
| Ethiopia | | 2.66 | 1.19 | 5.95 |
| Finland | 23.27 | 13.63 | 8.66 | 21.45 |
| France | 1.96 | 11.66 | 6.82 | 19.95 |
| Georgia | 1.47 | 4.43 | 2.48 | 7.93 |
| Germany | 7.56 | 10.25 | 6.24 | 16.86 |
| Ghana | | 1.49 | 0.54 | 4.12 |
| Greece | | 6.99 | 4.40 | 11.12 |
| Hungary | 24.79 | 173.76 | 22.81 | 1323.57 |
| India | | 2.17 | 0.94 | 5.01 |
| Indonesia | | 0.86 | 0.25 | 2.96 |
| Iraq | | 0.74 | 0.20 | 2.72 |
| Ireland | 3.55 | 15.75 | 9.73 | 25.48 |

| | | | | |
|---|---|---|---|---|
| Islamic Republic of Iran | | 0.80 | 0.23 | 2.83 |
| Israel | 0.18 | 2.97 | 1.20 | 7.32 |
| Italy | 0.33 | 2.46 | 0.94 | 6.47 |
| Jamaica | 0.49 | 3.21 | 1.58 | 6.52 |
| Japan | 0.32 | 3.50 | 1.73 | 7.08 |
| Kazakhstan | | 7.19 | 4.55 | 11.37 |
| Kenya | | 1.45 | 0.52 | 4.05 |
| Kyrgyzstan | 72.44 | 4.27 | 2.19 | 8.32 |
| Latvia | 168.25 | 18.03 | 10.80 | 30.11 |
| Lithuania | 39.76 | 56.15 | 21.16 | 148.98 |
| Luxembourg | 0.00 | 10.43 | 6.40 | 16.99 |
| Malaysia | | 1.37 | 0.47 | 3.98 |
| Malta | 2.83 | 4.34 | 2.19 | 8.60 |
| Mexico | 0.27 | 3.06 | 1.48 | 6.35 |
| Montenegro | | 8.24 | 5.18 | 13.09 |
| Morocco | 0.04 | 0.82 | 0.24 | 2.87 |
| Mozambique | | 1.57 | 0.58 | 4.27 |
| Nepal | | 1.27 | 0.44 | 3.67 |
| Netherlands | 1.29 | 2.99 | 1.15 | 7.78 |
| New Zealand | 4.28 | 5.95 | 2.89 | 12.28 |
| Nigeria | | 3.67 | 1.62 | 8.32 |
| Norway | 1.69 | 11.41 | 5.91 | 22.04 |
| Pakistan | | 0.72 | 0.19 | 2.67 |
| Peru | 0.00 | 10.78 | 5.93 | 19.58 |
| Philippines | | 3.76 | 1.93 | 7.33 |
| Poland | 14.81 | 24.74 | 13.50 | 45.34 |
| Portugal | 1.57 | 11.35 | 7.04 | 18.31 |
| Qatar | | 0.90 | 0.27 | 3.01 |
| Republic of Korea | | 12.69 | 7.92 | 20.34 |
| Republic of Moldova | 35.07 | 27.84 | 8.18 | 94.68 |
| Romania | 5.64 | 7.24 | 2.60 | 20.18 |
| Russian Federation | 164.14 | 224.08 | 32.49 | 1545.62 |
| Saudi Arabia | | 0.72 | 0.19 | 2.67 |
| Serbia | | 10.35 | 6.06 | 17.67 |
| Singapore | 0.66 | 1.10 | 0.36 | 3.37 |
| Slovakia | 20.23 | 29.44 | 12.94 | 66.98 |
| Slovenia | 33.96 | 38.12 | 13.61 | 106.82 |
| South Africa | | 8.59 | 5.55 | 13.31 |
| Spain | 0.68 | 3.63 | 1.35 | 9.75 |
| Sweden | 3.51 | 16.48 | 8.34 | 32.57 |
| Switzerland | 2.32 | 15.07 | 8.79 | 25.84 |
| Tajikistan | | 1.16 | 0.39 | 3.49 |
| Thailand | 0.00 | 5.20 | 3.04 | 8.92 |

| | | | | |
|---|---|---|---|---|
| The former Yugoslav Republic of Macedonia | | 3.72 | 1.71 | 8.09 |
| Turkey | 0.04 | 1.55 | 0.56 | 4.28 |
| Turkmenistan | | 4.30 | 2.22 | 8.35 |
| Uganda | | 11.54 | 7.11 | 18.73 |
| Ukraine | 88.44 | 11.93 | 6.07 | 23.45 |
| United Kingdom | 2.26 | 38.22 | 15.02 | 97.27 |
| United Republic of Tanzania | | 5.08 | 2.78 | 9.30 |
| United States of America | 2.00 | 11.61 | 6.96 | 19.34 |
| Uzbekistan | | 3.11 | 1.28 | 7.56 |
| Venezuela | 0.24 | 6.63 | 4.05 | 10.86 |
| Vietnam | | 5.98 | 3.64 | 9.82 |
| Yemen | | 0.72 | 0.19 | 2.68 |

Note. Predicted values based on results from negative binomial regression. In highlighted countries, observed and predicted values deviate by at least 10 deaths per 1,000,000 people. ACM = alcoholic cardiomyopathy deaths according to ICD-10 (code I42.6).

### 4.3.2 Step 2: Proportion of alcoholic cardiomyopathy deaths among all cardiomyopathy deaths

The proportion of ACM deaths among all CM deaths was predicted in Step 2 of Model 1. In addition to all observed proportions (*N*=50), **Table 4.3** contains all predicted (*N*=95) proportions, which ranged between 0.0% (Indonesia) and 86.0% (Belarus). Comparing the observed and predicted proportions, the mean absolute difference amounted to 4.7% (min: 0.0%, max: 30.0%, median: 1.9%), with 39 countries (78%; representing 95.8% of entire population with observed AAF data) within a +/- 5% range (countries beyond the threshold are highlighted in **Table 4.3**). Comparing countries within and beyond this threshold, we found that countries with large deviations between observed and predicted AAF had a similar GDP PPP ($34,811 versus $25,217; t-test: *p*=0.153) and comparable AUD prevalence (5.7% versus 6.4%; t-test: *p*=0.509). However, Eastern European (one country within threshold versus three countries beyond threshold; standardized deviation = 2.67) and Central Asian (zero countries within threshold versus two countries beyond threshold; standardized deviation = 2.72) countries were overrepresented in those countries beyond the threshold.

For the included countries, an unweighted mean AAF of 10.8% (95% CI: 10.3–11.4%) was predicted. The population weighted AAF based on predicted values only was estimated to be 7.1% (95% CI: 5.5–8.6%) of all CM deaths. Applying population weights to the combination of observed and predicted values, the mean AAF was calculated to be 6.9% (95% CI: 5.4–8.4%).

The results of sex-specific predictions (Model 2, Step 2) can be found in **Appendix A (study I)** (Additional file A.4; Sheets “Model 2 (female)” and “Model 2 (male)”). The weighted average AAF of observed and predicted proportions were estimated to be 2.9% (95% CI: 2.3–3.4%) and 8.9% (95% CI: 7.0–10.7%) for females and males, respectively.

The **Appendix A (study I)** (Additional file A.4) also presents results from Models 3 and 4, which incorporate the broader GBD definition of CM. Based on these models, the weighted average AAF combining observed and predicted proportions of ACM deaths among all CM deaths was estimated to be 5.9% (95% CI: 4.5–7.2%) for the entire population, 2.6% (95% CI: 2.0–3.1%) for females, and 7.9% (95% CI: 6.2–9.6%) for males.

**Table 4.3** Observed and predicted proportion of alcoholic cardiomyopathy deaths among all cardiomyopathy deaths, by country

| Country | Proportion in all CM deaths | | 95% Confidence interval | |
|---|---|---|---|---|
| | Observed | Predicted | Lower bound | Upper bound |
| Afghanistan | | 1.1% | 0.4% | 2.5% |
| Albania | | 9.4% | 4.0% | 19.0% |
| Algeria | | 1.1% | 0.4% | 2.5% |
| Argentina | 0.3% | 1.8% | 0.5% | 5.3% |
| Armenia | | 30.2% | 3.9% | 76.4% |
| Australia | 4.2% | 6.1% | 3.9% | 9.1% |
| Austria | 1.1% | 6.5% | 3.9% | 10.2% |
| Azerbaijan | | 27.6% | 2.8% | 76.3% |
| Bahrain | | 1.1% | 0.4% | 2.6% |
| Bangladesh | | 4.7% | 2.2% | 8.9% |
| Belarus | | 86.0% | 25.8% | 99.8% |
| Belgium | 4.3% | 5.2% | 3.7% | 7.2% |
| Bosnia and Herzegovina | | 9.5% | 4.1% | 19.0% |
| Brazil | 1.9% | 1.8% | 1.8% | 1.9% |
| Bulgaria | | 12.8% | 8.0% | 19.3% |
| Canada | 5.6% | 3.8% | 2.0% | 6.9% |
| Chile | 3.1% | 1.6% | 0.4% | 4.9% |
| China | | 5.7% | 3.4% | 9.0% |
| Colombia | 0.0% | 1.9% | 0.8% | 3.9% |
| Costa Rica | 3.6% | 1.8% | 0.7% | 3.9% |
| Croatia | 20.4% | 10.9% | 5.7% | 18.9% |
| Cyprus | 0.0% | 5.0% | 3.5% | 6.9% |
| Czech Republic | 5.9% | 9.7% | 4.6% | 18.1% |
| Democratic People's Republic of Korea | | 5.3% | 2.7% | 9.6% |
| Democratic Republic of the Congo | | 4.6% | 3.1% | 6.7% |
| Denmark | 10.3% | 5.0% | 3.5% | 7.0% |
| Egypt | | 0.7% | 0.1% | 2.9% |
| Estonia | 34.6% | 35.5% | 21.8% | 51.5% |
| Ethiopia | | 9.5% | 0.5% | 48.4% |
| Finland | 20.2% | 7.8% | 4.2% | 13.4% |
| France | 3.5% | 5.1% | 3.6% | 7.1% |
| Georgia | 5.1% | 34.4% | 5.4% | 78.9% |
| Germany | 7.7% | 5.7% | 3.8% | 8.3% |
| Ghana | | 8.5% | 0.5% | 42.4% |
| Greece | | 5.5% | 3.7% | 8.0% |

| | | | | |
|---|---|---|---|---|
| Hungary | 16.6% | 18.8% | 11.1% | 29.1% |
| India | | 7.1% | 1.3% | 24.0% |
| Indonesia | | 0.0% | 0.0% | 0.0% |
| Iraq | | 0.8% | 0.2% | 2.6% |
| Ireland | 8.3% | 5.9% | 3.9% | 8.5% |
| Islamic Republic of Iran | | 1.3% | 0.4% | 3.6% |
| Israel | 0.9% | 4.1% | 2.0% | 7.6% |
| Italy | 0.5% | 4.0% | 2.3% | 6.7% |
| Jamaica | 1.6% | 1.6% | 1.6% | 1.6% |
| Japan | 0.9% | 2.6% | 0.8% | 6.7% |
| Kazakhstan | | 37.7% | 6.5% | 81.3% |
| Kenya | | 4.4% | 2.4% | 7.5% |
| Kyrgyzstan | 80.2% | 50.2% | 12.4% | 87.8% |
| Latvia | 38.4% | 57.3% | 23.5% | 86.2% |
| Lithuania | 21.0% | 30.3% | 12.7% | 54.2% |
| Luxembourg | 0.0% | 4.9% | 3.4% | 6.8% |
| Malaysia | | 0.0% | 0.0% | 0.0% |
| Malta | 9.1% | 4.9% | 3.0% | 7.7% |
| Mexico | 2.5% | 1.7% | 0.7% | 3.6% |
| Montenegro | | 10.5% | 5.4% | 18.5% |
| Morocco | 1.8% | 1.1% | 0.4% | 2.6% |
| Mozambique | | 4.5% | 2.8% | 6.9% |
| Nepal | | 7.0% | 1.1% | 25.8% |
| Netherlands | 4.0% | 3.9% | 2.2% | 6.7% |
| New Zealand | 7.9% | 6.1% | 3.9% | 9.2% |
| Nigeria | | 5.6% | 2.2% | 12.1% |
| Norway | 6.3% | 5.2% | 3.3% | 7.8% |
| Pakistan | | 3.2% | 1.2% | 7.4% |
| Peru | 0.0% | 0.0% | 0.0% | 0.0% |
| Philippines | | 0.0% | 0.0% | 0.0% |
| Poland | 14.1% | 15.5% | 8.6% | 25.2% |
| Portugal | 4.4% | 6.2% | 2.9% | 12.0% |
| Qatar | | 1.4% | 0.3% | 4.8% |
| Republic of Korea | | 5.4% | 0.7% | 23.0% |
| Republic of Moldova | 55.0% | 27.0% | 9.0% | 54.6% |
| Romania | 2.8% | 10.2% | 4.7% | 19.6% |
| Russian Federation | | 65.9% | 32.5% | 89.9% |
| Saudi Arabia | | 0.6% | 0.1% | 3.3% |
| Serbia | | 11.4% | 6.3% | 18.8% |
| Singapore | 3.5% | 1.9% | 0.6% | 5.3% |
| Slovakia | 24.7% | 14.8% | 10.3% | 20.4% |
| Slovenia | 12.8% | 17.5% | 11.6% | 24.9% |
| South Africa | | 7.5% | 2.5% | 17.7% |
| Spain | 0.8% | 4.5% | 2.5% | 7.6% |
| Sweden | 8.6% | 6.1% | 4.1% | 9.0% |
| Switzerland | 5.9% | 5.5% | 3.8% | 7.8% |
| Tajikistan | | 36.5% | 4.8% | 83.5% |
| Thailand | 0.0% | 0.0% | 0.0% | 0.0% |

| | | | | |
|---|---|---|---|---|
| The former Yugoslav Republic of Macedonia | | 8.4% | 2.5% | 21.1% |
| Turkey | 0.4% | 1.1% | 0.4% | 2.6% |
| Turkmenistan | | 32.7% | 5.0% | 77.1% |
| Uganda | | 8.5% | 2.1% | 24.3% |
| Ukraine | | 35.2% | 18.6% | 55.3% |
| United Kingdom | 7.5% | 6.7% | 3.9% | 10.8% |
| United Republic of Tanzania | | 5.6% | 3.7% | 8.3% |
| United States of America | 2.2% | 4.0% | 2.0% | 7.2% |
| Uzbekistan | | 29.9% | 3.9% | 76.2% |
| Venezuela | 1.1% | 2.0% | 0.9% | 4.3% |
| Vietnam | | 0.0% | 0.0% | 0.0% |
| Yemen | | 0.7% | 0.1% | 2.9% |

Note. Predicted values based on results from fractional response probit regression. In highlighted countries, observed and predicted values deviate by at least 5 percentage points (absolute difference). ACM = alcoholic cardiomyopathy deaths according to ICD-10 (code I42.6). CM = cardiomyopathy deaths according to ICD-10 (code I42).

## 4.4 Discussion

We were able to estimate the AAF for CM, as well as for the GBD definition of CM. Altogether, the models fit reasonably well. However, we have identified several limitations.

In predicting the ACM crude mortality rate, marked deviations from observed values were detected for countries with high AUD prevalence and for some countries from Eastern Europe. In these countries, the observed ACM mortality rates varied more than in any other region. Take, for example, the three Baltic countries, Latvia, Estonia, and Lithuania. Here, variations in AUD prevalence (7.7–10.2%) and APC (12.0–17.9) clearly did not correspond to the variations in the observed ACM crude mortality rate (39.8–168.3). We acknowledge that other factors may be necessary for a more accurate modeling of ACM mortality in this region (see below for potential factors). However, for the remaining countries, we found the predictions to fit sufficiently.

In modeling of the primary outcome (AAF), accurate predictions were yielded for the majority of countries. However, similar to the first step, inaccurate estimates were pronounced among Eastern European countries in addition to Central Asian countries. Again, a large variation in observed AAF in these countries could not be sufficiently accounted for by the included covariates. While the observed and predicted AAF were highest in these countries (e.g., Kyrgyzstan: 80%, Moldova: 55%), they represent a relatively small share of the global population. Therefore, the proposed quantification was accurate (deviation of observed and predicted AAF <= 5%) for 95.8% of the examined population.

In order to understand the limitations of the model, one should have a closer look at the data sources. The first major limitation is related to ACM mortality data, which may be subject to coding errors. As persons with ACM are likely to have other end-organ damages, attribution of a person's death to a single disease category without any autopsy can be quite challenging (Tuusov et al., 2014); and then there is the attribution to alcohol as well (see next paragraph). In some former Soviet countries like Belarus (Kodeksy-by.com, 2017), Kyrgyzstan (Ministry of Justice of the Kyrgyz Republic, 2017), Russia (Leon, Shkolnikov, McKee, Kiryanov, & Andreev, 2010; Rg.ru, 2017), and Ukraine (Prostopravo.com.ua, 2017), autopsies are obligatory for many deceased people. While autopsies can determine CM as the cause of death, additional information is required on heavy drinking in order to identify ACM, e.g., via official AUD registries. However, in Russia, alcohol diagnoses either have to be established by an addiction medicine physician or require a documented history of alcohol use problems with the patient being formerly registered in the state-run addiction treatment system (Ivanova et al., 2013). Specifically, for the diagnosis of ACM, chronic alcoholism is one of the required criteria, which is why a substantial fraction of ACM deaths might be falsely coded as nonspecific CM (Semenova, Dubrovina, Gavrilova, Evdokushkina, & Gavrilov, 2005), as the physician conducting the autopsy may not always check for this information. As only two out of 10 people with AUD seek treatment worldwide (Kohn, Saxena, Levav, & Saraceno, 2004), this can be a source of bias in ACM mortality data, despite routinely performed autopsies.

Further and not restricted to ACM, there is a general problem with ICD-10 categories fully attributable to alcohol, i.e., those categories with "alcohol" or "alcoholic" in their names (World Health Organization, 1993). There is a high stigma attached to AUD (Room, 2005), even compared to other mental disorders (Schomerus et al., 2011). The specific stigma against AUD seems to have persisted over the past decades (Schomerus, Matschinger, & Angermeyer, 2014), even though medical treatment seems to be more acceptable (Schomerus, Matschinger, Lucht, & Angermeyer, 2014) and more people endorse a neuroscientific view of mental disorders, including AUD (Committee on the Science of Changing Behavioral Health Social Norms, Board on Behavioral Cognitive and Sensory Sciences, Division of Behavioral and Social Sciences and Education, & National Academies of Sciences Engineering and Medicine, 2016; Pescosolido, 2013). As a consequence of this rather universal stigma in our societies (Room, 2005), fully alcohol-attributable disease categories are likely to be underreported, as a number of studies have demonstrated. Most prominently, in a study in 12 cities in 10 countries, Puffer and Griffith (Puffer & Griffith, 1967) found that after triangulating data on death certificates with data from hospital records and interviews of attending physicians or family members, the number of deaths with alcoholic liver cirrhosis more than doubled, with the majority of new cases being detected under categories of cirrhosis that do not mention alcohol. This underreporting of alcoholic liver cirrhosis has persisted in later studies as well (Andreev & Zbarskaja, 2010; Haberman & Weinbaum, 1990; Prytz & Anderson, 1988; Tuusov et al., 2014), and it seems to be the case for all disease categories fully attributable to alcohol use (Pollock, Boyle, DeStefano, Moyer, & Kirk, 1987; Tuusov et al., 2014). More specifically for ACM, one study estimated the amount of underestimation to be about 30% (Prytz & Anderson, 1988).

As such, ACM mortality rates may have been underestimated due to stigma and coding problems. Despite these issues and the limited quality of WHO mortality data from some countries (C. D. Mathers, Fat, Inoue, Rao, & Lopez, 2005; Mikkelsen et al., 2015), we argue that using these data is still the best possible approach to obtain estimates of AAF for CM mortality. Trivially, we expect precision of our model to improve with a growing number of countries with vital registries and an increasing accuracy of reported mortality data (e.g., using autopsies to validate death certificates, see (Pagidipati & Gaziano, 2013)). However, autopsies alone will only be able to determine the alcoholic part or ACM in very few cases, and stigmatization of 100% alcohol-attributable diseases will remain a problem. Thus, it may be valuable to find and include stigmatization indicators in the model in the future to correct for stigmatization-attributable underestimations.

The second major limitation of our model is related to the degree of uncertainty inherited in aggregated alcohol measures. Accurate measurements of country-specific AUD rates are mostly lacking and have to be estimated instead. Moreover, these measurements are assessing a stigmatized disease through self-reports based on symptoms, which are culturally specific, thus introducing considerable bias in existing data (Rehm, 2016; Rehm, Anderson, et al., 2014). Total APC as an indicator has less bias, as it is mostly composed of sales, production, export, and import data, but the unrecorded component also may introduce significant bias (Rehm & Poznyak, 2015). In theory, the prediction model could be improved by using estimates for very heavy drinking over an extended period over time, but such data would need to be based on alcohol exposure of representative cohorts over decades, which simply do not exist.

## 4.5 Conclusion

Based on the crude mortality rate for ACM, AUD prevalence and APC per drinker, estimation of AAF for CM has been shown to be feasible through statistical modeling. However, limitations in data reliability and the limited knowledge of the relationship between alcohol and CM indicate that the proposed modeling strategy is only a first step towards a more comprehensive quantification of the global burden of ACM. We should strive to establish AAF based on exposure and RR (Rehm, Kehoe, et al., 2010; Walter, 1976, 1980), similar to the way it has been established for liver cirrhosis (Rehm, Taylor, et al., 2010) to avoid underestimation (Rehm, Samokhvalov, & Shield, 2013). However, this is a long-term solution, which will require cohort or case-control studies. In the meantime, we propose to apply the current methodology in order to determine the effects of alcohol consumption on CM in countries without observed AAF, even if it likely will be an underestimation.

# 5 Study II - National, regional and global mortality due to alcoholic cardiomyopathy in 2015


## Abstract

**Objectives** 1) A comprehensive mortality assessment of ACM and 2) examination of underreporting using vital statistics data. **Methods** A modelling study estimated sex-specific mortality rates for each country, which were subsequently aggregated by region and globally. Input data on ACM mortality were obtained from death registries for *N*=91 countries. For *N*=99 countries, mortality estimates were predicted using aggregate alcohol data from WHO publications. Descriptive additional analyses illustrated the scope of underreporting. **Results** In 2015, there were an estimated 25,997 (95% CI: 17,385-49,096) global deaths from ACM. This translates into 6.3% (95% CI: 4.2-11.9%) of all global deaths from CM being caused by alcohol. There were large regional variations with regard to mortality burden. While the majority of ACM deaths were found in Russia (19,749 deaths, 76.0% of all ACM deaths), for about one third of countries (*N*=57) less than one ACM death was found. Underreporting was identified for nearly every second country with civil registration data. Overall, two out of three global ACM deaths might be misclassified. **Conclusions** The variation of ACM mortality burden is greater than for other alcohol-attributable diseases, and partly may be the result of stigma and lack of detection. Misclassification of ACM fatalities is a systematical phenomenon, which may be caused by low resources, lacking standards and stigma associated with AUD. Clinical management may be improved by including routine alcohol assessments. This could contribute to decrease misclassifications and to provide the best available treatment for affected patients.

## 5.1 Introduction

CM refers to a heterogeneous group of diseases affecting the heart muscle (Richardson et al., 1996), where the heart muscle becomes enlarged, thick, or rigid. CM is one of the major heart disease categories, responsible for about 400,000 adult deaths (15+ years of age) per year globally and thus for 0.7% of all adult deaths (women: 0.7%; men 0.8%) and 2.2% of all cardiovascular deaths (women: 2.0%; men: 2.5) (World Health Organization, 2017a). Chronic heavy alcohol use is linked to dilated CM by ethanol acting as a toxin to weaken the heart muscle directly (see (Rehm, Hasan, et al., 2017) for the most recent review; (Rubin, 1979; Alvaro Urbano-Marquez et al., 1989) for early landmark studies; (Song & Rubin, 1972) for an experimental demonstration of the toxic effect of alcohol). One prominent description of what is now called ACM was by a Munich pathologist, who labeled the phenomenon the "Münchner Bierherz" (the Munich beer heart) and defined it as a disease characterized by cardiac dilatation and hypertrophy due to heavy consumption of beer over time (Bollinger, 1884). More recent research indicated that ACM is a specific form of dilated CM, caused by both ethanol (pure alcohol) and acetaldehyde, the first metabolite of ethanol, and that it can be worsened by interaction with other toxins, such as heavy metals, or by lack of nutrients (Klatsky, 2015).

Civil registration data are lacking for the majority of the world population (Mikkelsen et al., 2015) and ACM is too specific a cause that cannot by assessed via verbal autopsies as the alternative way of estimating causes of death. Thus, a systematic assessment of ACM mortality on a global scale requires mortality modelling for countries without available data (Manthey, Imtiaz, Neufeld, Rylett, & Rehm, 2017). Recently, ACM deaths and related disability have been included in the GBD mortality analyses for the first time (Naghavi et al., 2017). According to the GBD study, ACM has caused 81,600 global deaths in 2015. While these estimates provide an approximation of the true mortality burden attributable to ACM, only a proportion of these deaths might actually be recognized as such. As for other alcohol-attributable diseases (Pollock et al., 1987), it is likely that ACM is systematically misclassified at death.

This contribution aims 1) to provide a comprehensive epidemiological assessment of ACM mortality and 2) to examine the scope of underreporting. This study uses mortality data from countries with vital statistics to develop a statistical estimation model based on alcohol exposure. This model estimated the number of ACM deaths registered in 2015 for each country, for all regions, and globally. In order to allow for national and regional comparisons, mortality rates (number of ACM deaths per 1,000,000 adult population) and AAF (the proportion of all deaths from CM attributable to alcohol consumption) were calculated.

## 5.2 Methods

The methods used were developed and described in detail elsewhere (Manthey et al., 2017). We will restrict ourselves to sketching out the main modelling strategy here. The **Appendix B (study II)** contains more details on data definitions, the analytic strategy, and statistical modelling. Further, all data used for modelling purposes can be found in **Appendix B (study II)** (Additional file B.1).

### 5.2.1 Modelling strategy

Civil registration data on ACM deaths were available for *N*=91 countries. For the remaining countries (*N*=99), the sex-specific numbers of ACM deaths were estimated based on regression models, using APC, the prevalence of AUD, population size and the number of deaths from CM as predictors. After combining the recorded and estimated ACM mortality data, sex-specific mortality rates and AAF were calculated based on the ACM death counts for all countries (*N*=190), regions, and globally.

### 5.2.2 Additional analyses

Underreporting of ACM mortality in vital statistics was examined in two additional analyses. First, ACM mortality data directly available from vital statistics were compared to the model predictions. Second, all ACM mortality data – from vital statistics or from predictions – were compared to the GBD estimates.

### 5.2.3 Data sources

ACM mortality data were mainly obtained from the WHO mortality data base (World Health Organization, 2017c). The covariates were obtained from the Global Information System on Alcohol and Health ((World Health Organization, 2017b), APC) or the Global Status Report on Alcohol and Health ((World Health Organization, 2014), prevalence of AUD). For all countries, the number of CM deaths was obtained from the WHO Global Health Estimates data base (World Health Organization, 2017a) and comparative ACM mortality estimates were sourced from the GBD study (Naghavi et al., 2017). For all variables, data from the year 2015, or the last available year prior to 2015 were used.

## 5.3 Results

### 5.3.1 Distribution of alcoholic cardiomyopathy deaths

Globally, 25,997 people died from ACM in 2015 (women: 5,726; men: 20,272; see **Table 5.1** for regional distribution and CI). The majority of fatalities were heavily concentrated in the Eastern European region, where 80.1% of all deaths were estimated to occur. In Russia, 19,749 ACM deaths were recorded, which accounted for 76.0% of all global ACM deaths. In contrast, less than 1 ACM death was found for 57 countries.

With regard to mortality rates, a similar pattern was observed (see **Table 5.1**). Globally, the mortality rate was estimated at 4.9 deaths per 1,000,000 adults (women: 2.1; men: 7.6). However, in most regions (18 out of 21) and countries (159 out of 190) mortality rates were below the global average. In 110 countries, less than 1 adult in 1,000,000 was estimated to die from ACM. Mortality rates above 10 deaths per 1,000,000 people were observed in 23 countries. Only in Central and Eastern Europe, the average mortality rates exceeded 10 per 1,000,000. The largest mortality rates were observed in Russia (163.8 per 1,000,000). **Figure 5.1** illustrates the distribution of mortality rates across all countries.

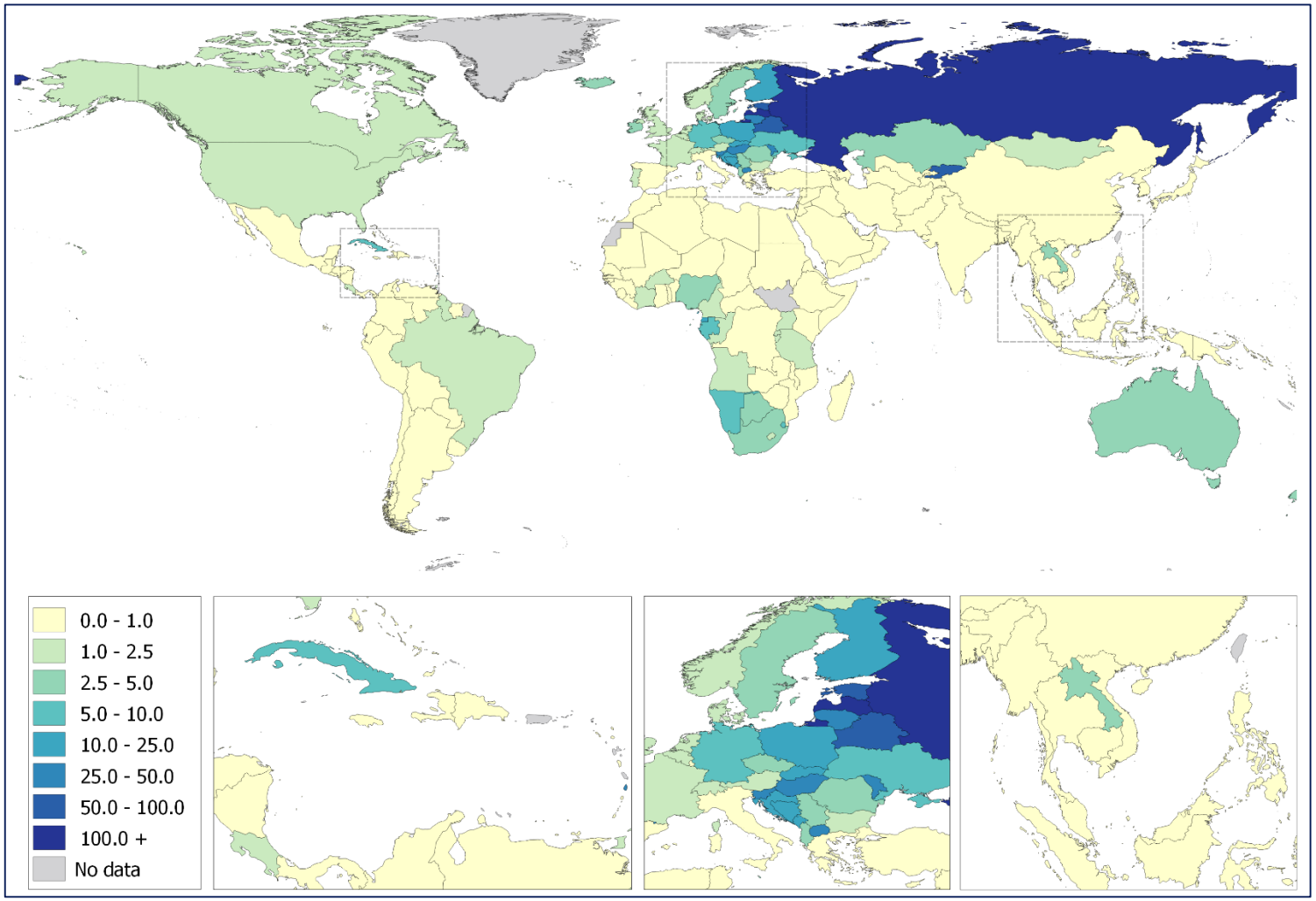


**Figure 5.1** Alcoholic cardiomyopathy mortality rates (deaths per 1,000,000 adult population) in 2015. Mortality rates denote the number of deaths per 1,000,000 adult population.

**Table 5.1** Regional and global distribution of deaths due to alcoholic cardiomyopathy and of mortality rates by sex

| Region | Number of ACM deaths | | | Mortality rate | | |
|---|---|---|---|---|---|---|
| | total | female | male | total | female | male |
| Andean Latin America | 2 (0-17) | 1 (0-8) | 1 (0-9) | 0.1 (0.0-0.5) | 0.1 (0.0-0.4) | 0.1 (0.0-0.5) |
| Australasia | 73 (42-124) | 10 (0-31) | 63 (42-93) | 3.2 (1.8-5.5) | 0.8 (0.0-2.7) | 5.6 (3.8-8.2) |
| Caribbean | 94 (86-129) | 6 (4-24) | 88 (82-104) | 3.4 (3.1-4.7) | 0.5 (0.3-1.8) | 6.5 (6.1-7.8) |
| Central Asia | 323 (300-365) | 58 (54-66) | 265 (246-298) | 5.1 (4.8-5.8) | 1.7 (1.6-2.0) | 8.7 (8.1-9.8) |
| Central Europe | 1,101 (554-2,874) | 194 (64-841) | 907 (522-2,033) | 11.2 (5.6-29.2) | 3.8 (1.3-16.5) | 19.2 (11.1-43.0) |
| Central Latin America | 48 (35-89) | 3 (1-17) | 45 (35-72) | 0.3 (0.2-0.5) | 0.0 (0.0-0.2) | 0.5 (0.4-0.8) |
| Central Sub-Saharan Africa | 56 (31-104) | 17 (7-41) | 39 (24-63) | 0.9 (0.5-1.7) | 0.5 (0.2-1.3) | 1.3 (0.8-2.1) |
| East Asia | 242 (104-585) | 20 (4-94) | 222 (100-491) | 0.2 (0.1-0.5) | 0.0 (0.0-0.2) | 0.4 (0.2-0.8) |
| Eastern Europe | 21,007 (14,972-37,380) | 5,029 (4,341-8,193) | 15,978 (10,658-29,472) | 119.8 (85.4-213.1) | 52.6 (45.4-85.7) | 200.2 (133.5-365.6) |
| Eastern Sub-Saharan Africa | 140 (92-221) | 19 (9-42) | 120 (82-179) | 0.7 (0.4-1.1) | 0.2 (0.1-0.4) | 1.2 (0.8-1.8) |
| High-income Asia Pacific | 48 (3-166) | 2 (0-45) | 46 (11-122) | 0.3 (0.0-1.1) | 0.0 (0.0-0.6) | 0.6 (0.2-1.7) |
| High-income North America | 585 (218-1,450) | 93 (7-374) | 492 (211-1,076) | 2.0 (0.8-5.1) | 0.6 (0.1-2.6) | 3.5 (1.5-7.6) |
| North Africa and Middle East | 50 (18-166) | 17 (5-70) | 33 (13-95) | 0.1 (0.0-0.4) | 0.1 (0.0-0.4) | 0.2 (0.1-0.5) |
| Oceania | 3 (1-10) | 2 (0-7) | 1 (0-3) | 0.5 (0.2-1.6) | 0.6 (0.2-2.2) | 0.4 (0.2-1.1) |
| South Asia | 92 (41-213) | 6 (2-30) | 85 (40-184) | 0.1 (0.0-0.2) | 0.0 (0.0-0.1) | 0.2 (0.1-0.3) |
| Southeast Asia | 96 (43-234) | 17 (6-62) | 79 (39-173) | 0.2 (0.1-0.5) | 0.1 (0.0-0.3) | 0.4 (0.1-0.7) |
| Southern Latin America | 23 (5-135) | 1 (0-41) | 22 (6-94) | 0.5 (0.1-2.8) | 0.0 (0.0-1.6) | 0.9 (0.3-4.0) |
| Southern Sub-Saharan Africa | 179 (108-299) | 21 (10-44) | 159 (99-255) | 3.4 (2.1-5.7) | 0.8 (0.4-1.6) | 6.1 (3.8-9.9) |
| Tropical Latin America | 260 (112-565) | 20 (2-72) | 240 (111-493) | 1.6 (0.7-3.5) | 0.2 (0.0-0.9) | 3.0 (1.4-6.3) |
| Western Europe | 974 (251-2,875) | 145 (13-994) | 830 (275-1,881) | 2.7 (0.7-8.1) | 0.8 (0.1-5.5) | 4.8 (1.6-10.9) |
| Western Sub-Saharan Africa | 602 (341-1,094) | 45 (17-134) | 556 (325-960) | 2.7 (1.5-5.0) | 0.4 (0.1-1.2) | 5.0 (2.9-8.7) |
| Global | 25,997 (17,358-49,096) | 5,726 (4,548-11,230) | 20,272 (12,920-38,150) | 4.9 (3.2-9.2) | 2.1 (1.7-4.2) | 7.6 (4.8-14.2) |

Note. Mortality rates denote the number of deaths per 1,000,000 adult population. Definition of regions are based on the Global Burden of Disease study (Naghavi et al., 2017).

### 5.3.2 Distribution of alcohol-attributable fractions

The regional estimates of AAF and their CI are presented in **Table 5.2**. Globally, 6.3% of all deaths from CM were attributable to alcohol (women: 3.1%%; men: 9.0%). The geographical distribution of AAF was similar to the distribution of mortality rates. In the vast majority of regions (19 out of 21) and countries (166 out of 190) AAF were below the global average. In 103 countries AAF were below 1%. Only in 21 countries, more than 10% of all CM deaths were caused by alcohol. On the regional level, AAF above 10% were found only in Eastern Europe. The largest AAF was found in Kyrgyzstan (67.9%). **Figure 5.2** illustrates the distribution of AAF across all countries. As AAF variation was largest in European and Central Asian countries, these regions are additionally highlighted in **Figure 5.3**.

For a complete list of ACM deaths, mortality rates and AAF by sex and country, see **Table B.3**.

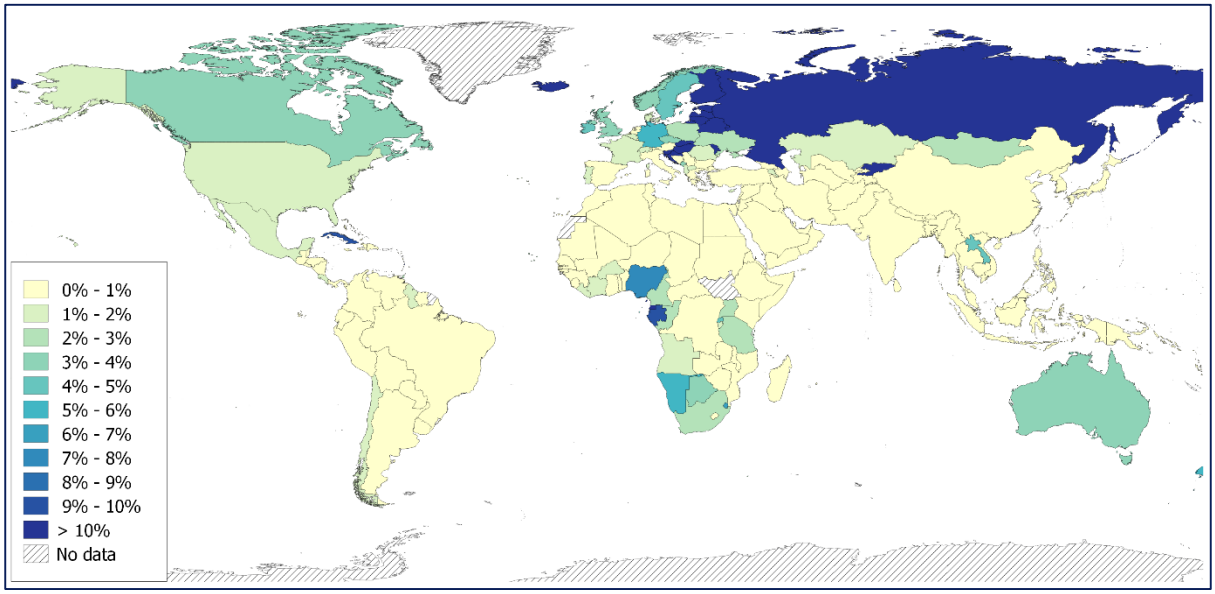


**Figure 5.2** Alcohol-attributable fractions of cardiomyopathy deaths for the total adult population in 2015. Alcohol-attributable fraction denotes the proportion of alcoholic cardiomyopathy deaths among all deaths due to cardiomyopathy, myocarditis or endocarditis.

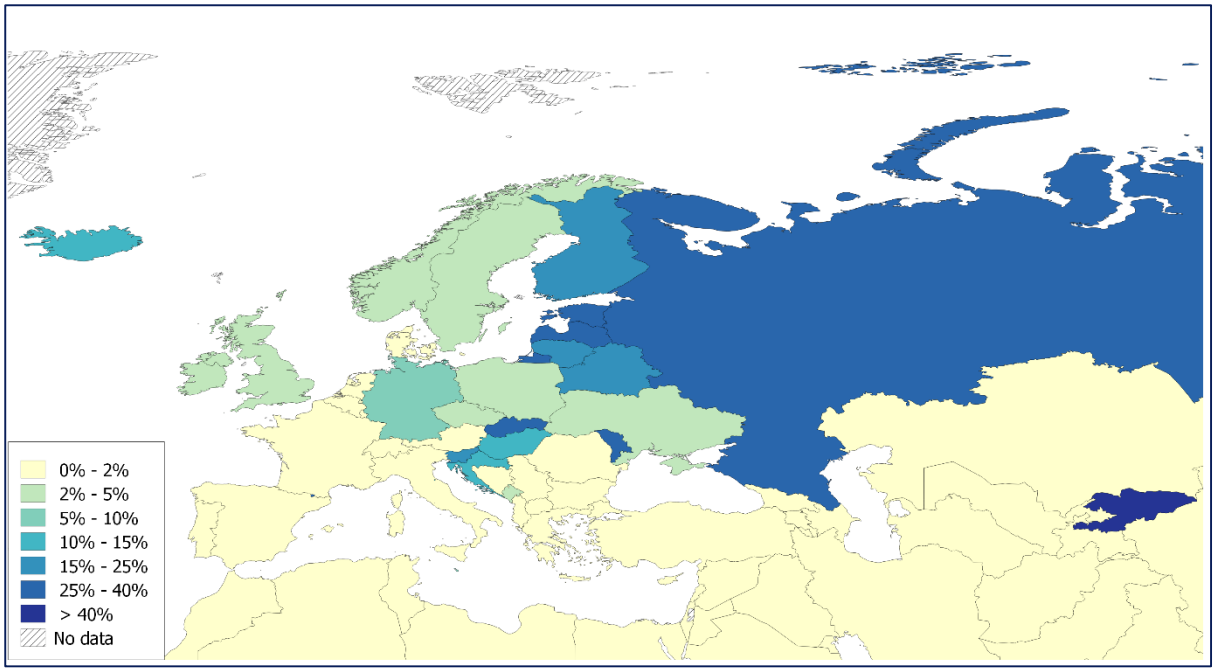


**Figure 5.3** Alcohol-attributable fractions of cardiomyopathy deaths for the total adult population in 2015 for selected countries in Europe and Central Asia. Alcohol-attributable fraction denotes the proportion of alcoholic cardiomyopathy deaths among all deaths due to cardiomyopathy, myocarditis or endocarditis.

### 5.3.3 Additional Analysis

Comparing civil registration mortality data with predicted fatalities from our models, indications for underreporting (i.e. recorded deaths were lower than predicted lower limits) were identified for 44 out of 91 countries (women: 33; men: 42; for full results see **Table B.4**). In total, 2,505 deaths were potentially underreported in the identified geographies. Underreported fatalities were concentrated on few countries (43.1% of potentially underreported deaths from Romania, Serbia, France).

In **Table B.5**, ACM deaths from vital statistics or respectively modelled data (main findings of this study) are contrasted with estimates from the GBD study for each country. For the vast majority of countries (*N*=172 out of 190), a higher number of ACM fatalities were reported in the GBD study (median difference = 21 deaths). Globally, there were 55,465 more deaths according to GBD estimates as compared to the findings produced from civil registration data alone.

**Table 5.2** Regional and global distribution of alcohol-attributable fractions by sex

| Region | Alcohol-attributable fraction | | |
|---|---|---|---|
| | **total** | **female** | **male** |
| Andean Latin America | 0.1% (0.0-0.9%) | 0.1% (0.1-0.9%) | 0.1% (0.0-0.8%) |
| Australasia | 4.4% (2.6-7.5%) | 1.6% (0.1-4.9%) | 6.2% (4.2-9.2%) |
| Caribbean | 4.3% (3.9-5.9%) | 0.6% (0.4-2.5%) | 7.2% (6.8-8.6%) |
| Central Asia | 8.8% (8.2-9.9%) | 4.7% (4.4-5.4%) | 10.9% (10.1-12.2%) |
| Central Europe | 2.4% (1.2-6.4%) | 0.8% (0.3-3.5%) | 4.3% (2.5-9.6%) |
| Central Latin America | 0.9% (0.7-1.8%) | 0.2% (0.0-0.8%) | 1.5% (1.2-2.5%) |
| Central Sub-Saharan Africa | 1.1% (0.6-2.1%) | 0.7% (0.3-1.6%) | 1.7% (1.0-2.7%) |
| East Asia | 0.6% (0.3-1.6%) | 0.1% (0.0-0.5%) | 1.3% (0.6-2.8%) |
| Eastern Europe | 24.1% (17.2-42.9%) | 16.6% (14.3-27.1%) | 28.0% (18.7-51.3%) |
| Eastern Sub-Saharan Africa | 1.3% (0.9-2.1%) | 0.4% (0.2-0.9%) | 2.1% (1.4-3.1%) |
| High-income Asia Pacific | 0.5% (0.01.7%) | 0.0% (0.0-0.9%) | 1.0% (0.2-2.6%) |
| High-income North America | 1.8% (0.7-4.4%) | 0.7% (0.0-2.6%) | 2.5% (1.1-5.7%) |
| North Africa and Middle East | 0.1% (0.0-0.4%) | 0.1% (0.0-0.4%) | 0.2% (0.1-0.5%) |
| Oceania | 0.5% (0.2-1.5%) | 0.5% (0.1-1.9%) | 0.4% (0.2-1.1%) |
| South Asia | 0.4% (0.2-1.1%) | 0.1% (0.0-0.3%) | 0.8% (0.4-1.7%) |
| Southeast Asia | 0.3% (0.2-0.9%) | 0.2% (0.1-0.5%) | 0.6% (0.3-1.2%) |
| Southern Latin America | 0.3% (0.1-2.0%) | 0.0% (0.0-1.3%) | 0.7% (0.2-2.8%) |
| Southern Sub-Saharan Africa | 2.5% (1.5-4.2%) | 0.6% (0.3-1.3%) | 4.2% (2.6-6.7%) |
| Tropical Latin America | 1.4% (0.6-3.1%) | 0.3% (0.0-0.9%) | 2.2% (1.0-4.6%) |
| Western Europe | 2.7% (0.7-7.9%) | 0.9% (0.1-6.2%) | 4.1% (1.4-9.3%) |
| Western Sub-Saharan Africa | 4.1% (2.4-7.5%) | 0.7% (0.3-2.0%) | 7.1% (4.1-12.3%) |
| Global | 6.3% (4.2-11.9%) | 3.1% (2.4-6.0%) | 9.0% (5.7-16.7%) |

Note: Alcohol-attributable fraction denotes the proportion of alcoholic cardiomyopathy deaths among all deaths due to cardiomyopathy, myocarditis or endocarditis. Definition of regions are based on the Global Burden of Disease study (Naghavi et al., 2017).

## 5.4 Discussion

### 5.4.1 Mortality pattern

There are two major findings that should be highlighted. First, about every 15$^{th}$ death from CM around the globe was estimated to be attributable to alcohol consumption in 2015. This estimate is in line with previous estimates ranging between 3% and 40% (M. R. Taylor, Carniel, & Mestroni, 2006). Second, the burden of ACM is heavily concentrated on a few countries from Eastern Europe and Central Asia. While in these countries 22.0% of all global CM deaths were found, they accounted for 82.0% of all global ACM deaths.

The presented mortality pattern is generally reflecting the global pattern in alcohol-attributable disease burden (World Health Organization, 2014), but the described variability between high and low burden countries appears to be much greater for ACM mortality than for most other alcohol-attributable causes of deaths. One important explanatory factor may be related to different levels and patterns of alcohol consumption impacting on various diseases (Rehm, Gmel, et al., 2017). While ACM incidence has been mainly linked to very heavy alcohol consumption over an extended period of time (Rehm, Hasan, et al., 2017), much lower levels of ethanol intake are associated with increased risk of various cancers, liver cirrhosis and hypertension (Rehm, Gmel, et al., 2017). Thus, a considerable number of alcohol-attributable deaths can be observed around the world, even in countries where alcohol consumption levels are relatively low (World Health Organization, 2014). However, as high levels of alcohol use are rare in most countries, few ACM fatalities in these countries are not surprising.

Conversely, the heavy aggregation of ACM deaths in Eastern European can partially be explained by high drinking levels in this region. Traditionally, alcohol use in these countries was higher than elsewhere in Europe or globally, with very heavy binge occasions characterizing the local drinking culture (Popova, Rehm, Patra, & Zatonski, 2007; Shield, Rylett, & Rehm, 2016). Accordingly, the high ACM mortality burden in Eastern Europe can be regarded as the result of a unique combination of detrimental drinking patterns and alcohol exposure in a wide range of adults during the past two decades. However, decreasing alcohol consumption in these countries and an overall harmonization of drinking patterns in Europe as observed in the past few years (Shield et al., 2016), should result in a reduction of ACM deaths in this region in the coming years.

There is another unique feature to Eastern European countries relevant to explain the excessive ACM fatalities in this region. In some former Soviet countries including Belarus, Kyrgyzstan, Russia, and Ukraine, autopsies have been legally required for deceased persons under a certain age threshold (Manthey et al., 2017). As autopsies are vital for recognizing CM (described in detail below) and form an important step in classification of ACM as cause of death, detection rate of ACM might be above average in these countries. Taken together, the observed mortality gap between Eastern European countries and the remaining European region could be attributable to higher alcohol consumption and better detection.

### 5.4.2 Implications of mortality underreporting

There are good reasons to assume that the presented figures are likely to represent only the lower end of the actual mortality burden related to ACM. Most importantly, the presented results are only based on registered deaths, for which the cause of death was unequivocally determined to be ACM. However, misclassification of ACM deaths is likely as cause of death ascertainment can be impaired in various ways. Briefly, there are two strong prerequisites to classifying ACM as the main cause of death: 1) Identification of dilated CM, and 2) knowledge of the deceased persons' drinking habit over a lengthy period of time, which allows to attribute the dilation to excessive alcohol use.

With regard to the first requirement, identifying dilated CM as main cause of death, is not an ordinary task. Here, two scenarios can be thought of: cases with a CM diagnosis preceding death and cases with a sudden cardiac death (i.e. no lifetime CM diagnosis). Dilated CM in live patients can be indicated by rather unspecific symptoms, such as abdominal pain, fatigue, or nausea but formal diagnosis get only confirmed via echocardiography, magnetic resonance imaging and/or histological analyses (Weintraub et al., 2017). For individuals who died from a sudden cardiac death, an analogue diagnostic workup may not be feasible. First, sudden cardiac death might not be identified as such (due to drownings, traffic fatalities, etc.). Second, imaging techniques may be established as a viable alternative in the future (Blokker, Wagensveld, Weustink, Oosterhuis, & Hunink, 2016) but autopsy remains the gold standard in identifying the underlying cause of death to date. However, autopsies as well as imaging techniques are far from being routinely applied to deceased persons in most countries, due to lack of resources or ethical considerations.

As outlined, there are numerous barriers in identifying dilated CM as the main cause of death but none of the required diagnostics can determine its specific etiology. In fact, the second prerequisite to classify ACM implies that the patients' drinking habit needs to be reviewed as one possible cause for dilated CM. While the guidelines of the American Heart Association specify 'a significant history of alcohol use' (Bozkurt et al., 2016), there is no unambiguous cutoff for a diagnostic decision (Rehm, Hasan, et al., 2017). This uncertainty, in addition to the severe stigma associated with AUD (Schomerus et al., 2011), may deter physicians from enquiring into the patients' alcohol use in detail. For deceased persons, acquiring the required information is even more challenging as physicians would need to consult their kin and/or review medical files for an indication of heavy alcohol use (e.g. addiction ward admission).

As outlined there are possible errors for ascertainment of ACM as cause of death, but studies on other alcohol-attributable diseases indicate that misclassification is a systematic phenomenon (Daula & Hanzlick, 2006; Pollock et al., 1987). As information collected during management of previous diseases are often used to issue death certificates, possible diagnostic errors can be carried forward and thus contribute to false cause of death classifications. In fact, cause of death ascertainment in ACM patients is particularly challenging as multiple competing diseases may need to be considered because affected patients are at high risk for other potentially fatal conditions due to their high drinking levels (Rehm, Gmel, et al., 2017). In a US study, chronic alcohol use was often omitted from death certificate when other natural diseases were present in the deceased person (Daula & Hanzlick, 2006).

While these are good reasons to assume that ACM deaths are underreported in vital statistics, there is also empirical support for this claim. First, the GBD study resulted in nearly three times more global ACM deaths as compared to the presented results in this study by accounting for misclassifications in vital statistics. However, the GBD estimates cannot account for all potential misclassification errors outlined above, i.e. the true extent of ACM mortality might be even greater.

Second, there are large variations between countries regarding civil registration, which cannot be explained by alcohol exposure. Based on the models in this study, indications for underreporting could be found for nearly half of countries with vital statistics. For example, Hungary and Serbia are very similar in terms of alcohol exposure and population size but the gap in ACM deaths is inexplicably wide (Hungary: 221 deaths, Serbia: 20 deaths). Thus, ACM misclassification is likely a greater problem in countries identified as low-end outliers in our models.

### 5.4.3 Clinical implications

The extent of misclassification of ACM deaths suggests that this condition is not only underdiagnosed but also undertreated. The presented figures illustrate where interventions are urgently needed. As ACM is preceded by very high drinking levels over several years (Rehm, Hasan, et al., 2017), strategies should aim at keeping drinking levels low. One efficient way would be through alcohol screening and subsequent interventions, which was advocated to be implemented routinely in primary health care (OECD, 2015). As high drinking levels associated with ACM incidence also imply increased risk for incidence of other conditions (Rehm, Gmel, et al., 2017), it is plausible to assume that individuals at risk for ACM seek help in various health care settings. This is supported by European studies indicating that people with AUD are overrepresented in primary care settings as compared to the general population (Manthey et al., 2016) and high risk drinkers are more prone to be admitted to inpatient and emergency services than light drinkers (Miquel et al., 2018).

The quantification of mortality rates can also be of use for facilitating the diagnostic decision-making process. If dilated CM has been diagnosed, it is essential to ascertain the specific cause in order to provide the best treatment. This is especially relevant for ACM as reduction of their drinking levels or complete abstinence is the best way to increase survival rates (Bozkurt et al., 2016). According to recommendations from the American Heart Association (Bozkurt et al., 2016), information from various sources need to be gathered to rule out potential etiologies. The ideal workup is reasonably complex and involves a lot of data synthesis, which could cause physicians to resort to non-analytical, intuitive heuristic approaches instead (Berner & Graber, 2008; van den Berge & Mamede, 2013). However, these heuristics are overly impacted by cognitive errors, availability and confirmation bias and they often lead to premature diagnostic decisions and thus to diagnostic errors (van den Berge & Mamede, 2013). These errors have been identified by comparing diagnoses with autopsy reviews yielding misclassification rates between 10% and 15% in various medical fields (Berner & Graber, 2008), while much higher rates have been reported for alcohol-attributable diseases (Daula & Hanzlick, 2006; Pollock et al., 1987). There are numerous reasons for diagnostic errors (for a review, see (van den Berge & Mamede, 2013)), but knowledge gaps resulting in underestimating the impact of alcohol consumption on various diseases may be responsible for insufficient management of alcohol. These knowledge gaps could be closed by informing physicians about the quantified impact of alcohol on CM. Presenting country- and sex-specific attributable fractions of alcohol and other risk factors for dilated CM in future guidelines could help fostering analytical reasoning and balancing the diagnostic workup. This measure is particularly important in countries with large degree of ACM underreporting.

### 5.4.4 Conclusion

This study provides a comprehensive assessment of ACM mortality burden, which is heavily concentrated on Eastern European countries. However, vital statistics death counts are likely underestimates with two out of three ACM fatalities being misclassified. The results imply that the condition is currently underdiagnosed and undertreated, which adds to previous claims to implement routine screening and interventions to reduce alcohol-attributable mortality burden. An improved ACM management can contribute to decrease diagnostic errors and to provide the best available treatment.

### 5.4.5 Limitations

The interpretation of the results should consider the degree of uncertainty of the input data sources. Specifically, bias in both CM and ACM mortality data cannot be excluded due to great variations in availability and quality of mortality data across countries (Mikkelsen et al., 2015). ACM mortality data were mainly available from high-income countries and no data were available from Sub-Saharan countries. As underreporting may constitute a major bias in the recorded ACM deaths, the presented figures should be considered lower bound estimates. It should be acknowledged that differences in the age structure of the underlying populations are not reflected in the presented mortality rates, which can introduce a bias in regional comparisons using these figures. Technically, a more extensive modelling strategy with sex- and age-group specific models would have allowed age-standardization of the mortality rates. However, such models would have required age-specific alcohol exposure indicators (i.e. prevalence of AUD) data, which are hardly available for most low and middle-income countries, and estimation would have introduced another element of uncertainty. These models would also need to consider that incidence of ACM in a given age group depends on alcohol exposure in the previous age group, due to the considerable the time lag between heavy drinking over time and development of ACM (Rehm, Hasan, et al., 2017). Importantly, the main focus of this contribution was not to compare mortality rates across locations but to quantify the country-and region-specific mortality burden. As these study objectives could be well met with results from sex-stratified models, we decided to perform sex-specific models only.

# 6 Study III - Mortality from alcoholic cardiomyopathy: Exploring the gap between estimated and civil registry data


## Abstract

**Background** Based on civil registries, 26,000 people died from ACM in 2015 globally. In the GBD 2017 study, garbage coded deaths were redistributed to ACM, resulting in substantially higher ACM mortality estimates (96,669 deaths, 95% CI: 82,812–97,507). We aimed to explore the gap between civil registry and GBD mortality data, accounting for alcohol exposure as a cause of ACM. **Methods** ACM mortality rates were obtained from civil registries and GBD for *N*=77 countries. The relationship between registered and estimated mortality rates was assessed by sex and age groups, using Pearson correlation coefficients, in addition to comparing mortality rates with population alcohol exposure—the underlying cause of ACM. **Results** Among people aged 65 years or older, civil registry mortality rates of ACM decreased markedly whereas GBD mortality rates increased. The widening gap of registered and estimated mortality rates in the elderly is reflected in a decrease of correlations. The age distribution of alcohol exposure is more consistent with the distribution of civil registry rather than GBD mortality rates. **Conclusions** Among older adults, GBD mortality estimates of ACM seem implausible and are inconsistent with alcohol exposure. The garbage code redistribution algorithm should include alcohol exposure for ACM and other alcohol-attributable diseases.

## 6.1 Introduction

Heavy alcohol use is a major contributor to CVD (O'Keefe, DiNicolantonio, O'Keefe, & Lavie, 2018; Rehm & Roerecke, 2017). Among other conditions, high levels of alcohol use can lead to ACM, which is characterized by a dilation and impairment of the left ventricle (Mirijello et al., 2017). While this condition is the result of the toxic effects of alcohol, the symptoms and clinical presentation are not unique to ACM but largely resemble other dilated CM (Weintraub et al., 2017). As with other CM, ACM is associated with systolic dysfunction and a considerable risk factor for myocardial infarctions and sudden death (Guzzo-Merello et al., 2014; Weintraub et al., 2017). In the past few years, interest on ACM grew as reflected in the publication of several reviews describing clinical presentations (Guzzo-Merello et al., 2014), pathophysiological mechanisms (Piano & Phillips, 2014), as well as the causal relationship between heavy alcohol consumption and incidence of ACM (Rehm, Hasan, et al., 2017).

For most alcohol-attributable conditions, mortality is estimated via AAF based on alcohol exposure and risk relations. For ACM, however, this method cannot be applied to due to a lack of data quantifying the risk relations (Rehm, Hasan, et al., 2017). Hence, an alternative method was proposed (Manthey et al., 2017), based on cause of death data reported by countries with civil registration of vital statistics (Mikkelsen et al., 2015); these vital statistics were available for 91 countries and formed the basis to model ACM as cause of death for all countries and globally (Manthey, Probst, Rylett, & Rehm, 2018). According to these estimates, there were 25,997 global deaths from ACM in 2015. Applying a different methodology, the GBD 2017 study resulted in a more than three-fold mortality figure (90,669 deaths in 2015, 95% CI: 82,812–97,507) (Institute for Health Metrics and Evaluation, 2018a). Higher GBD estimates were the result of redistributing so called garbage coded deaths to well-defined cause of death codes, including ACM and other CVD (Roth et al., 2018). The term garbage code has first been coined in 1996 and refers to all codes, which are not useful for public health analyses (Murray et al., 1996; Naghavi et al., 2010). More precisely, the term encompasses all codes that are not recognized by the ICD-10 (World Health Organization, 1993) in describing the actual underlying cause of death. Instead, garbage codes may indicate a symptom (e.g., pain) or an intermediate cause of death, such as heart failure (HF, (Snyder et al., 2014)).

The outlined gap in ACM mortality estimates warrants further attention given the large difference and because GBD mortality estimates are susceptible to the methods employed in redistributing garbage coded deaths, as previously demonstrated for ischemic heart disease (Wan & Yang, 2017). In this contribution, we sought to further explore the gap between registered and estimated ACM deaths. For this purpose, we used mortality data from civil registries, which serve as one main input for the GBD study, and compare these data with mortality estimates as published in the last GBD update (Roth et al., 2018). We aimed to examine the association of registered and estimated ACM mortality rates in countries with available civil registry data. Further, we compared ACM mortality distributions to the distribution of alcohol exposure—its underlying cause by definition. In sensitivity analyses, we examined associations of ACM and garbage coded deaths, which constitute the base for redistributing garbage codes to well-defined causes of death in the GBD study (Roth et al., 2018).

## 6.2 Experimental section

### 6.2.1 Description of data sources and disease definitions

We obtained adult (15 years or older) mortality data from two sources: (1) civil registration data from the WHO mortality database (World Health Organization, 2018c), and (2) estimated mortality data from the GBD 2017 study (Institute for Health Metrics and Evaluation, 2018a).

From the WHO mortality database, we retained all country-years with any four-digit ICD-10 code and available data on sex and age. After matching the ICD-10 codes (World Health Organization, 1993) with the disease categories as defined in the GBD 2017 study, we obtained country-, year-, sex-, and age-specific mortality data for the following categories: CVD, CM and myocarditis (hereafter referred to as 'all CM'), ACM, as well as CVD and HF garbage codes (for the definition of each category, see **Appendix C (study III)** and (Institute for Health Metrics and Evaluation, 2018b)). We calculated the death counts for a new cause of death category 'all CVD' from the sum of CVD and CVD garbage code cause of death definition. For country-years with mortality data available only for one sex, we assumed 0 deaths for the other sex. From the GBD database, we obtained the estimated mortality data for the same disease categories (except for garbage codes) (Institute for Health Metrics and Evaluation, 2018a).

The two mortality data sets were then matched on the above given disease categories and all country-years with available mortality data on ACM and HF garbage codes from civil registries were retained, resulting in a total number of 77 countries (with 823 country-years). In order to calculate mortality rates (i.e., deaths per 100,000 adults) we combined the mortality data with population estimates from the United Nations Population Division (Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, 2017). Alcohol exposure was defined as intake of pure alcohol per adult (in liters per year, APC). Alcohol exposure data were obtained from a recent modeling study using WHO sources and forecasting techniques (Manthey et al., 2019). Alcohol exposure data was not available for all 5-year age bands, which required the aggregation of mortality data into the available age groups. In addition to same-year, 5-year and 10-year lagged alcohol exposure estimates were calculated to account for the estimated lag time between exposure and disease incidence (Rehm, Hasan, et al., 2017). These lag times are in line with findings of a recent review and clinical guidelines (Bozkurt et al., 2016; Rehm, Hasan, et al., 2017).

### 6.2.2 Descriptive analyses

For descriptive analyses, we only used data from the most recent available year per country (n = 77 data points by sex and age group). For both registered and estimated deaths, we calculated death counts and age-standardized mortality rates per 100,000 adults. To illustrate the gap between registered and estimated deaths, we calculated the ratio of estimated to registered deaths and mortality rates (the larger the ratio, the larger the gap). To examine the association of registered and estimated ACM deaths, Pearson correlations were computed for all adults and by sex and age.

### 6.2.3 Sensitivity analyses

In sensitivity analyses, we aimed to test whether ACM deaths and garbage coded deaths were negatively associated. In the GBD study, a negative association between garbage coded deaths and target diseases is the requirement for the redistribution models (Ahern et al., 2011; Naghavi et al., 2010; Roth et al., 2018). In brief, these models assume that in jurisdictions with accurate coding practice, a low proportion of deaths are assigned to garbage codes and all other diseases are accurately coded. Consequently, a negative association indicates that the fewer deaths being assigned to garbage codes, the more deaths are being accurately coded. In the GBD study, a negative association between garbage coded deaths and a given cause of death is used as indicator for the redistribution of garbage coded deaths, while positive or non-significant associations indicate that garbage coded deaths may not be redistributed to the given disease.

In this contribution, we performed similar regression models using proportion of ACM deaths among all CVD deaths as target disease and proportion of HF deaths among all CVD deaths as garbage codes. We selected HF deaths as they were cited as source for redistributing deaths to ACM in the GBD 2017 study (Roth et al., 2018). Furthermore, in previous studies the redistribution of HF deaths has resulted in an increase of deaths attributable to CM (Ahern et al., 2011; Snyder et al., 2014), which should theoretically increase the number of ACM deaths, as well.

Poisson regression models examined the relationship of HF garbage coded deaths (independent variable) and ACM deaths (dependent variable), allowing for random intercepts in each country. As opposed to GBD redistribution models, we included APC as additional covariate, which was identified as main driver for estimating ACM mortality (Manthey et al., 2018). Further, we allowed for nonlinear associations by including polynomials of the independent variable. For more details on the sensitivity analyses, see **Appendix C (study III)**.

All analyses were conducted with R version 3.5.1 (R Core Team, 2018).

## 6.3 Results

A descriptive summary of the mortality data compiled for this study can be found in **Table 6.1**.

**Table 6.1** Registered and estimated deaths by disease category and sex

| GBD Disease Definition | Absolute Number of Deaths | | | Age-Standardized Mortality Rate [1] | | |
|---|---|---|---|---|---|---|
| | Women | Men | Both sexes | Women | Men | Both sexes |
| Cardiovascular diseases | | | | | | |
| Registered [2] | 1,396,965 | 1,469,004 | 2,865,969 | 89.1 | 148.3 | 116.1 |
| Estimated [2] | 2,459,266 | 2,386,248 | 4,845,514 | 154.9 | 239.3 | 193.6 |
| Ratio [3] | 1.8 | 1.6 | 1.7 | 1.7 | 1.6 | 1.7 |
| Cardiomyopathy and myocarditis | | | | | | |
| Registered [2] | 8,240 | 11,938 | 20,178 | 0.6 | 1.4 | 1.0 |
| Estimated [2] | 66,730 | 75,616 | 142,346 | 4.4 | 8.0 | 6.1 |
| Ratio [3] | 8.1 | 6.3 | 7.1 | 6.8 | 5.9 | 6.2 |
| Alcoholic Cardiomyopathy | | | | | | |
| Registered [2] | 538 | 3,345 | 3,883 | 0.1 | 0.4 | 0.2 |
| Estimated [2] | 3,589 | 18,894 | 22,483 | 0.3 | 2.1 | 1.2 |
| Ratio [3] | 6.7 | 5.6 | 5.8 | 5.8 | 5.4 | 5.3 |
| Cardiovascular garbage codes | | | | | | |
| Registered [2] | 963,461 | 780,529 | 1,743,990 | 58.4 | 77.1 | 67.2 |
| Estimated [2] | / | / | / | / | / | / |
| Ratio [3] | / | / | / | / | / | / |
| Heart failure garbage codes | | | | | | |
| Registered [2] | 283,222 | 209,033 | 492,255 | 15.8 | 20.0 | 17.8 |
| Estimated [2] | / | / | / | / | / | / |
| Ratio [3] | / | / | / | / | / | / |

Note: Based on *N*=77 countries, see **Additional file C.1** for a detailed list of the included countries. [1] Age-standardized number of deaths per 100,000 adults. [2] All deaths obtained from in civil registries (World Health Organization, 2018c) or as estimated in the GBD 2017 study (Institute for Health Metrics and Evaluation, 2018a). [3] Ratio of estimated to registered deaths.

### 6.3.1 Epidemiology of registered and estimated alcoholic cardiomyopathy mortality

Using data from the most recent available year for each country, data from N=77 countries could be obtained, representing 1.54 billion adults, mainly living in the Americas and WHO European Region (for a summary on included countries key data, see **Additional file C.1**). Since 1990, 63,016 ACM deaths (females: 8816; males: 54,200) were recorded in civil registries. For the same set of countries during the same period, the GBD study estimated the ACM death count at 370,675 (females: 66,080; males: 304,595). Thus, for each registered ACM death, nearly 5 additional deaths have been estimated in the GBD study for the included countries (female ratio: 7.5; male ratio: 5.6). For all CM, the gap between estimated to registered deaths is similar to ACM (female ratio: 8.1; male ratio: 6.3), but it is considerably lower for deaths from all CVD (female ratio: 1.8; male ratio: 1.6).

While the variation by sex was relatively low, there were substantial differences in the distribution of estimated and registered deaths across all ages by cause of death definition. In **Figure 6.1**, the registered and estimated mortality rates are presented by sex and across all 5-year age groups (see **Appendix C (study III)** for mortality rates by cause, sex, and age). The age distribution of registered and estimated deaths was largely parallel for CVD, with largely constant ratios of estimated to registered mortality rates across all age groups (1.5–2.0). For all CM, distribution of registered and estimated mortality rates were similar, with exponential increases in older age groups. The ratios of estimated and registered mortality rates for all CM were closer among 15 to 59 year olds (2.4–4.7) and increased in older ages (75 years or older: 9.1–11.4).

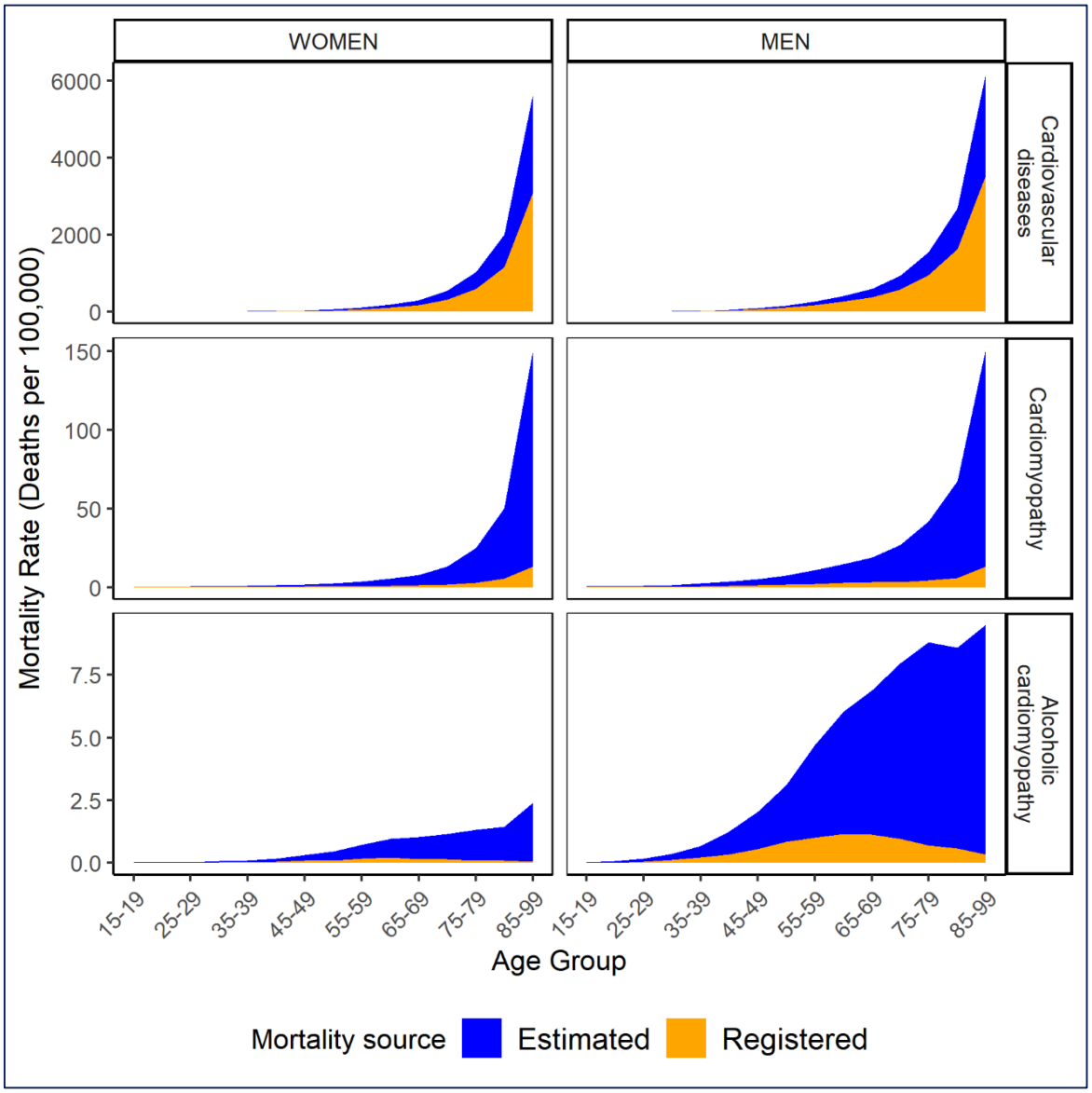


**Figure 6.1** Mortality rates of registered (orange) and estimated (blue) deaths over the life span by cause of death definition (rows) and sex (columns); based on most recent available mortality data from *N*=77 countries.

In contrast, the age distribution of registered and estimated mortality rates of ACM diverged substantially. While registered mortality rates largely resemble a normal distribution peaking at ages 60–64 (0.7 deaths per 100,000 adults) and decreasing thereafter, the estimated ACM mortality rates were left-skewed and peaked in the oldest age group (4.7 deaths per 100,000 people aged 85+ years). Consequently, the gap between estimated and registered mortality rates widened with increasing age, with lowest ratios among 25 to 64 year olds (3.2–5.0) and highest ratios in older ages (75 years and older: 13.1–33.4).

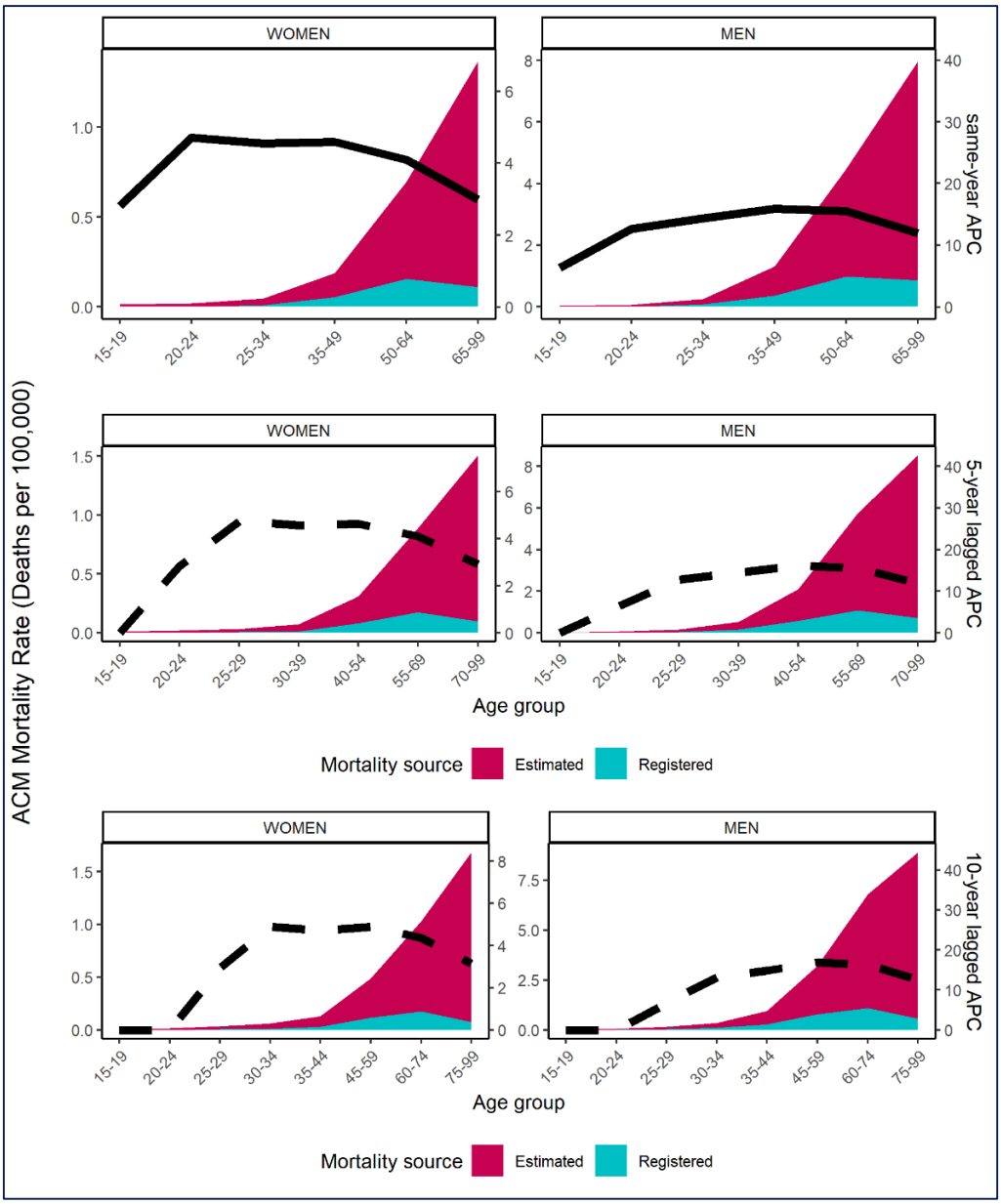


**Figure 6.2** Estimated (red) and registered (blue) alcoholic cardiomyopathy (ACM) mortality rates per 100,000 and alcohol per capita consumption (APC) over selected age groups and by sex (column) for most recent available data of *N*=77 countries; solid line denotes same-year APC (first row) and dashed line denotes 5-year (second row) and 10-year lagged APC (third row).

The diverging age pattern in ACM mortality figures can also be observed in **Figure 6.2**, where registered and estimated mortality rates are presented together with alcohol exposure estimates, for available age groups. The plot suggests that the age distribution of alcohol exposure was more congruent with registered rather than estimated ACM mortality rates. Among older age groups, both registered mortality rates for ACM and alcohol exposure decreased, while the estimated mortality rates increased. Similar patterns can be observed for both same-year, 5-year, and 10-year lagged alcohol exposure.

The age-dependent association of registered and estimated ACM deaths is also presented in **Table 6.2**. The correlation of registered and estimated ACM mortality rates was high among all adults for both women and men. Among men, high correlations (>0.55) can be observed for all ages between 20 and 79 years. In older age groups, the correlations were below 0.20. Among women, registered and estimated ACM mortality rates were not associated in the youngest (25–29 years) and oldest (75 and older) age groups, but were associated in the age groups in between. Furthermore, and among both sexes, the association was most pronounced (i.e., >0.7) up to 64-year old people and decreases thereafter.

**Table 6.2** Correlation of registered and estimated alcoholic cardiomyopathy crude mortality rates (deaths per 100,000 people) for all adults and by sex and age groups.

| | **Women** | **Men** |
|---|---|---|
| All Adults | 0.796 (0.697 to 0.866)** | 0.917 (0.872 to 0.946)** |
| By age group | | |
| 15–19 | NA | NA |
| 20–24 | NA | 0.968 (0.95 to 0.979)** |
| 25–29 | 0.212 (−0.012 to 0.416) | 0.985 (0.977 to 0.991)** |
| 30–34 | 0.42 (0.217 to 0.589)** | 0.988 (0.981 to 0.992)** |
| 35–39 | 0.731 (0.607 to 0.821)** | 0.956 (0.932 to 0.972)** |
| 40–44 | 0.779 (0.672 to 0.854)** | 0.963 (0.942 to 0.976)** |
| 45–49 | 0.955 (0.93 to 0.971)** | 0.941 (0.908 to 0.962)** |
| 50–54 | 0.956 (0.932 to 0.972)** | 0.764 (0.652 to 0.844)** |
| 55–59 | 0.815 (0.723 to 0.879)** | 0.777 (0.67 to 0.853)** |
| 60–64 | 0.899 (0.845 to 0.935)** | 0.901 (0.848 to 0.936)** |
| 65–69 | 0.305 (0.087 to 0.495)* | 0.545 (0.366 to 0.685)** |
| 70–74 | 0.513 (0.326 to 0.661)** | 0.73 (0.605 to 0.82)** |
| 75–79 | 0.184 (−0.042 to 0.391) | 0.618 (0.458 to 0.74)** |
| 80–84 | 0.099 (−0.127 to 0.316) | 0.158 (−0.069 to 0.369) |
| 85–99 | 0.025 (−0.2 to 0.247) | 0.136 (−0.091 to 0.349) |

Note: Based on most recent available data from *N*=77 countries, see **Additional file C.1** for a detailed list of the included countries; * $p<0.01$; ** $p<0.001$; NA = correlations could not be calculated due to zero registered deaths.

### 6.3.2 Sensitivity Analyses

Results of sensitivity analyses are illustrated in **Figure 6.3** (for model results, see **Appendix C (study III)**). Between proportion of ACM deaths and proportion of HF deaths among all CVD deaths, there was a non-monotonous negative association. Only for very low proportions of HF deaths among all CVD deaths (below 5%) could a decrease in the proportion of ACM deaths among all CVD deaths be observed.

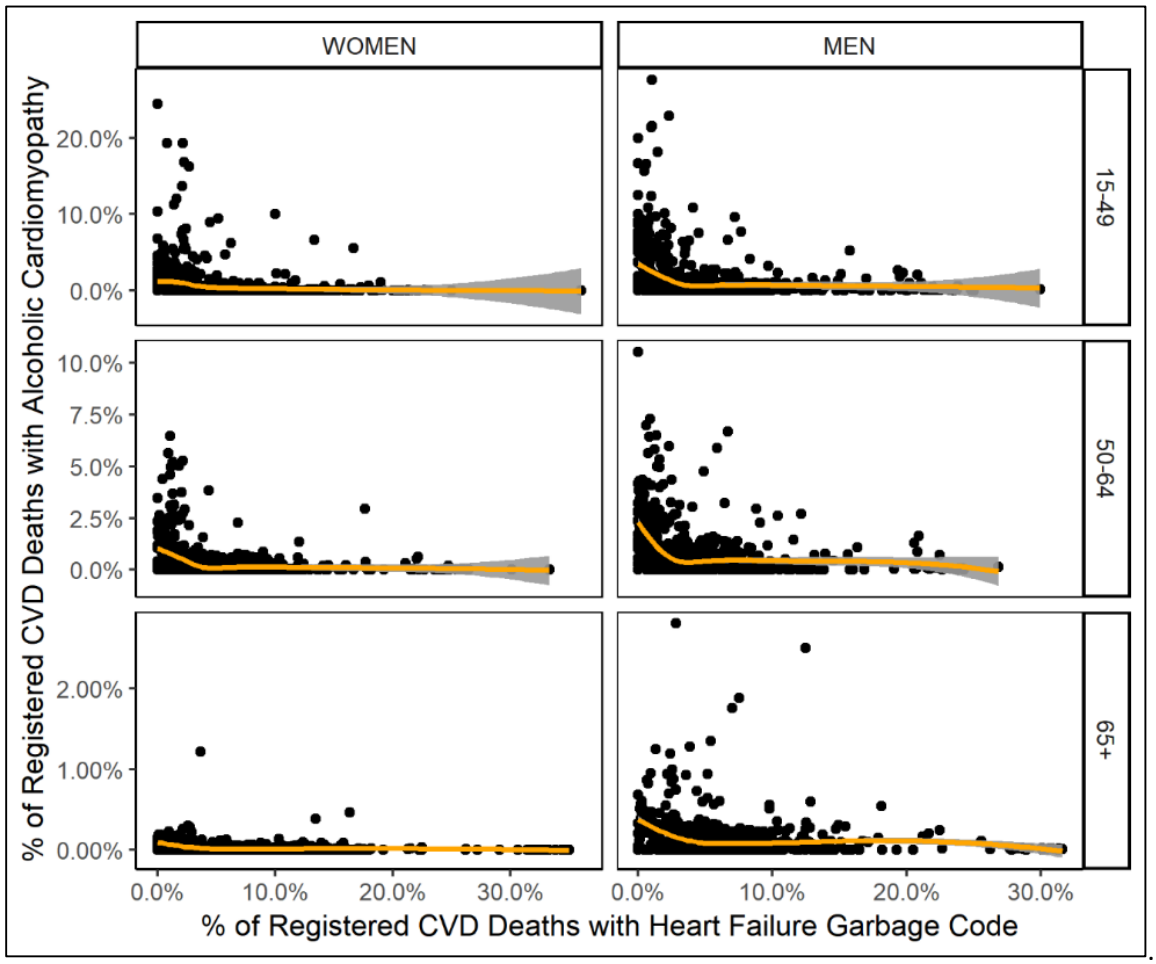


**Figure 6.3** Scatter plots of proportion of heart failure garbage code deaths and proportion of alcoholic cardiomyopathy deaths among all cardiovascular disease (CVD) deaths by sex (column) and age group (row); orange line denotes the smoothing function of fitted proportion of alcoholic cardiomyopathy deaths among all CVD deaths obtained from multi-level models.

## 6.4 Discussion

### 6.4.1 Summary of the findings

This study compared mortality data from civil registries with estimates from the GBD 2017 study, using data from *N*=77 countries.

The GBD mortality estimates of ACM seem implausible for the elderly population. Among people aged 65 years or older, the registered ACM mortality rates follow a decrease in alcohol exposure, which is the core determinant of ACM. A similar age distribution of ACM has also been identified in a recent study examining hospitalization data of the United States of America (Ram et al., 2018). In contrast, the estimated ACM mortality rates continue to increase with an ageing population. Given a decrease in alcohol exposure among the elderly, an increase of ACM mortality in people aged 65 years or older is unlikely and may result in overestimating the total number of ACM deaths in the GBD study.

### 6.4.2 Improving alcoholic cardiomyopathy mortality estimates

For other alcohol-attributable diseases, mortality is estimated using AAF, which are calculated from exposure and risk functions (for global mortality estimates, see reference (World Health Organization, 2018b); for a summary of risk functions, see reference (Rehm, Gmel, et al., 2017)). As AAF are stratified by age groups, the decline in exposure in the elderly population can be reflected in lower AAF in these age groups. For ACM, mortality in the GBD study is estimated by redistributing garbage coded deaths, yet without accounting for age variations in alcohol exposure (Ahern et al., 2011; Roth et al., 2018).

In our view, ACM mortality estimates should be made consistent with alcohol exposure, because this is its core determinant. Further, reductions of alcohol use have been associated with improvements of the clinical course of ACM (Guzzo-Merello et al., 2015), including mortality risks (Fauchier et al., 2000). In order to align alcohol exposure and ACM mortality estimates in the GBD study, alcohol exposure data should be included in models estimating redistributing proportions for ACM. As indicated in this study, a 5-year or 10-year lag of alcohol exposure may prove useful in redistribution models, which likely represents the period of heavy alcohol intake required to develop ACM (Bozkurt et al., 2016; Rehm, Hasan, et al., 2017). While a 5-year period of heavy chronic drinking has been used as lower bound to develop ACM (Lazarević et al., 2000; Prazak, Pfisterer, Osswald, Buser, & Burkart, 1996), up to 25 years of heavy chronic drinking among affected patients have been reported in a number of clinical studies (Cerqueira, Harp, Ritchie, Stratton, & Walker, 1991; Lazarević et al., 2000; Regan et al., 1969). However, such long lag times may capture treatment onset rather than disease incidence, similar to the delay between onset and treatment of AUD (Chapman, Slade, Hunt, & Teesson, 2015). Thus, in the absence of data from population studies, we proposed to use a 10-year lag to model disease onset until further confirmative data is available. Among 15–24 year olds, a 10-year lag would result in 0 ACM deaths, which is largely in line with the registered deaths and is coherent with alcohol-attributable mortality estimation for cancer (World Health Organization, 2018b).

### 6.4.3 The impact of garbage code redistribution for alcoholic cardiomyopathy mortality estimates

In the GBD study, garbage coded deaths are redistributed to other well-defined diseases, including ACM. Since GBD 2013, redistribution proportions are estimated to redistribute garbage coded deaths to selected target diseases (the method proposed in reference (Ahern et al., 2011); for details of application see Appendix 1 of reference (Roth et al., 2018)).

Unfortunately, cause-specific results of the redistribution models are not available, thus, it remains unknown how many of the estimated ACM deaths have been redistributed from which garbage code. However, HF deaths have been cited as one out of three garbage codes which were redistributed to ACM in the GBD study (Roth et al., 2018). Further, HF deaths account for a substantial share of CVD deaths in civil registry data and several studies have proposed methods to redistribute HF deaths (Ahern et al., 2011; Foreman, Naghavi, & Ezzati, 2016; Naghavi et al., 2010; Snyder et al., 2014). In brief, HF describes an impaired functioning of the heart muscle and is an intermediate state between death and the actual underlying cause, which can be CVDs (e.g., CM, ischemic heart disease) but also other non-communicable diseases such as chronic respiratory diseases, diabetes, or cirrhosis (Foreman et al., 2016; Roth et al., 2018).

Results from our sensitivity analyses suggest that HF deaths may not be redistributed to ACM in the majority of countries included in this study. This is in line with previous studies showing only marginal—if any—increases of mortality from all CM after redistributing HF garbage codes (Ahern et al., 2011; Snyder et al., 2014). In GBD, senility and atherosclerosis have been referred to as other garbage codes, which were redistributed to CVD, including ACM (Roth et al., 2018). More details on the misclassification of cause of deaths codes should be provided in the GBD study to improve clinical care and cause of death coding practice. For ACM, this is particularly important as five out of six deaths may not be recognized.

### 6.4.4 Clinical relevance

There is a large gap between registered and estimated deaths due to ACM but also due to all other CM. Primarily, a large number of deaths assigned with garbage codes may be the result of inaccurate cause of death coding. However, this gap could also be an indicator for suboptimal clinical care (detection, treatment) during a lifetime. To diagnose ACM, clinicians need to identify a dilated heart muscle, rule out other potential causes, and conduct an extensive assessment of the patients' alcohol use (Bozkurt et al., 2016; Mirijello et al., 2017). However, the substantial stigma around alcohol dependence (Schomerus et al., 2011) may deter clinicians from such conversations with their patients, as reported in primary care (Hanschmidt et al., 2017). Clinicians may further be discouraged to have discussions around alcohol with their patients because of several uncertainties with this topic, e.g., the differential impact on diseases—especially for CVD, for which both beneficial and detrimental effects have been observed (for an overview of risk functions, see reference (Rehm, Gmel, et al., 2017)), the fact that there is no recognized "safe" level of alcohol consumption (for a recent discussion, see references (Abat, Roussel, Chaudet, & Raoult, 2019; Griswold & Gakidou, 2019; Shield & Rehm, 2019)), or the lack of an international consensus in defining risky drinking (Furtwaengler & de Visser, 2013).

However, even if all ACM cases were accurately identified in clinical practice (i.e., no garbage codes), the contribution of alcohol may still be underestimated if based on death certificates only (Pollock et al., 1987). In summary, vital statistics may be the best available data source to estimate ACM mortality to date. Yet, prospective studies on the relationship between alcohol intake and incidence of CM are required to yield more accurate mortality estimates.

### 6.4.5 Strengths and limitations

This study used mortality data from 77 countries, representing the majority of high-income countries with highly accurate data from civil registries (Mikkelsen et al., 2015). However, countries without such data are not represented in this study, most notably African and Asian countries. Thus, the presented results may not apply to non-Caucasian populations from low- and middle-income countries. Further, we restricted the sensitivity analyses to HF, which was cited as major source for garbage code redistribution for ACM. As ACM-specific results from the algorithm that redistributes garbage codes in the GBD 2017 study are not available, the impact of redistributing other garbage codes to ACM mortality could not be determined in this study. As the alcohol exposure data used in the GBD study are not available to the authors, we used data from a recent modeling study based on WHO collection and estimation of APC per country, which is considered the most valid estimate of overall alcohol exposure (Gmel & Rehm, 2004), and was validated by country representatives (Poznyak et al., 2013). This has limited the breakup of mortality data to age groups, for which alcohol exposure data is available.

### 6.4.6 Conclusions

GBD mortality estimates of ACM are implausible for adults aged 65 years or older, as they are incongruent with civil registry and alcohol exposure data in this age group. In order to produce more consistent ACM mortality estimates, the redistribution algorithms in the GBD study should be aligned with alcohol exposure data.

# 7 General discussion

## 7.1 Summary of the findings

Looping back to the three aims of this dissertation, it was firstly demonstrated how the contribution of alcohol consumption to mortality from CM can be estimated using available civil registry data. In essence, the models served to estimate AAF in countries without any ACM mortality data using the link between population alcohol exposure and mortality from any CM. Comparisons of registered and estimated ACM mortality rates and AAF suggest the results to be robust for most regions (see **study I**).

Secondly, the global burden of ACM was estimated using civil registry data from 91 countries, suggesting that about 26,000 persons died from ACM in 2015. This translates into 6.3% of all CM deaths being attributable to alcohol consumption, globally. Notably, the distribution of the mortality burden of ACM is heavily skewed, with 3 out of 4 ACM deaths recorded in Russia and in nearly no ACM deaths in one third of all countries. However, the mortality figures are likely underestimates as there was evidence for underreporting in a substantial number of countries. Further, a comparison with GBD estimates suggests that ACM mortality burden may be three times as high as estimated in this dissertation (see **study II**).

Thirdly, comparing mortality data from civil registries and GBD estimates indicate that only one in six ACM deaths were accurately coded on death certificates, with the remaining deaths being assigned ill-defined cause of death codes, such as HF. However, the study also suggests GBD mortality estimates to be overestimates in the older population, as the estimated death rates are inconsistent with the main driver of ACM – alcohol exposure – in persons aged 75 years or older. Drawing upon the findings of this study, measures to improve garbage code redistribution algorithms to produce more consistent ACM mortality estimates have been proposed (see **study III**).

## 7.2 Strengths and limitations

This dissertation provided the first global assessment of ACM mortality and the relative contribution of alcohol consumption to mortality from CM for nearly 200 countries. Moreover, this dissertation paved the way to include ACM in the global alcohol-attributable disease burden for the first time (World Health Organization, 2018b). While the presented ACM mortality estimates and AAF are based on a set of most reliable data sources, there are several limitations to the data sources and the proposed methodology, which should be acknowledged when interpreting these estimates. These limitations and their implications are outlined in the following.

### 7.2.1 Coverage of civil registry data

Limited coverage of available civil registry data to upper-middle and high-income countries constitutes a major limitation of the findings. For instance, global ACM mortality was estimated without any civil registry data from a single Sub-Saharan African country (**study II**). Based on the proposed methodology (**study I**), the link between any CM mortality, alcohol exposure and ACM mortality was examined in countries with available civil registry data and subsequently applied to all remaining countries. This method assumes a consistent link that can be generalized across regions. However, as illustrated in **study I** and **study II**, some Eastern European and Central Asian countries have unexpectedly high rates of ACM, with AAF well above 50%, which could not be fully explained with the available covariates. In locations without available civil registry data, ACM mortality may not correspond to the patterns identified in the regression models. It should further be noted that this uncertainty is not fully captured in the uncertainty estimates of the findings.

### 7.2.2 Quality of death reporting and the role of garbage codes

In the WHO mortality data base, "data are included only for countries reporting data properly coded according to the International Classification of Diseases" (p. 2, (World Health Organization, 2019c)). However, in the data base documentation, "cross-national differences in coding practices, particularly in the use of codes for ill-defined and unknown causes" are explicitly noted (p. 10, (World Health Organization, 2019c)). In fact, the use of ill-defined causes, such as HF or 'malignant neoplasm of unspecified site', is inconsistent with the ICD-10 (or its predecessors), as those codes merely describe an intermediate cause of death, but not the actual underlying driver of death (Murray et al., 1996). These ill-defined causes fall under the umbrella term 'garbage codes', which are widely used classifying deaths (e.g., HF is the fourth most frequently reported cause of death in Germany (Stolpe & Stang, 2019)), with detrimental effects for the quality of mortality data (Mikkelsen et al., 2015).

As illustrated in **study III**, the GBD study estimates that for every ACM death recorded in civil registries, five ACM deaths are falsely assigned other, presumably ill-defined codes. While this gap might in reality be smaller given the indicated overestimates of ACM mortality in older adults, a substantial underreporting of ACM in civil registries seems very likely. This has the following implications on the findings in this dissertation: First, the underreporting of ACM mortality in civil registries suggests that the actual ACM mortality burden is substantially higher than estimated in **study II.** Second, the underestimation of ACM mortality might be more pronounced in lower- as compared to higher-income countries as higher rates of garbage codes have been recorded in lower- -income countries (C. Mathers, Stevens, Mahanani, Fat, & Hogan, 2018). Third, underreporting also impacts on AAF, but the effect largely depends on the redistribution of garbage codes to both ACM and other CM. According to results from **study III**, garbage codes are more often redistributed to other CM than to ACM, thus resulting in proportional larger increases of the denominator than the nominator in **Equation 3.1**. This, in turn, may imply that AAF might actually be smaller than estimated in **study II**. However, as the analyses in **study III** were restricted to (middle- and high-income) countries with available civil registry data, global inferences are not feasible.

### 7.2.3 Classification of alcohol-attributable deaths

While the outlined problems of death coding do affect all CM (see **section 7.3.1**), there are some additional concerns related to the validity of deaths ascribed to ACM and other alcohol-attributable diseases. As there are no pathophysiological features specific to ACM, the only way to diagnose ACM is to rule out potential causes of an idiopathic dilated CM, including alcohol and other toxins (Bozkurt et al., 2016; Mirijello et al., 2017). The problem, however, is, that guidelines or objective criteria to ascertain the contribution of alcohol to CM do not exist. While acute and short term alcohol exposure can be determined using laboratory markers (e.g. phosphatidyl ethanol; (Maisch, 2016)), ACM is the result of a prolonged period of heavy drinking, for which there is no simple biological marker or even consensus on the minimum length of the required period of sustained alcohol intake (Rehm, Hasan, et al., 2017). While the literature converges on the improvement of cardiac functions after reducing alcohol consumption (Guzzo-Merello et al., 2014; Guzzo-Merello et al., 2015; Mirijello et al., 2017), this hardly classifies as diagnostic criterion, especially for deceased persons. The vague und unstandardized diagnostic workup of ACM may contribute to uneasy feelings of physicians when discussing alcohol use with their patients (Hanschmidt et al., 2017), which may be attributed to the severe stigma attached to AUD (Schomerus et al., 2011). This is not restricted to interactions with living patients but may also be a problem in issuing death certificates (Pollock et al., 1987). As ACM cases are highly comorbid (e.g., 48% with hypertension, 31% with chronic pulmonary disease, see (Ram et al., 2018)), diagnostic and treatment capacities might be diverted from ACM to other diseases, which could further impair recognition of ACM. Given these circumstances, it is not surprising that three out of four ACM cases are not recognized during lifetime (Hietanen et al., 2019).

In light of this evidence, it is likely that alcohol is often disregarded as cause for an identified idiopathic dilated CM among both living and deceased persons. Consequently, the proportion of ACM deaths among CM deaths (i.e. AAF) is likely being underestimated in civil registries. The AAF estimates presented in **study I** and **study II** should therefore be interpreted with caution as they might indicate the lower bound of the actual contribution of alcohol to CM.

## 7.3 Implications for future research

This dissertation has several implications for future research, which are outlined in the following.

### 7.3.1 Contribution of alcohol to cardiomyopathy

For the majority of diseases, the contribution from alcohol is quantified based on prospective cohort, historical cohort, or case-control studies, linking alcohol intake to disease incidence, morbidity, or mortality at a later point in time (for a summary of studies linking alcohol use to hypertension as example, see (B. Taylor et al., 2009)). Given the lack of epidemiological studies, this approach was not found to be feasible for CM (Rehm, Hasan, et al., 2017). While the alternative approach presented in this dissertation has been found to produce consistent and meaningful estimates, this method will cease to be feasible in the foreseeable future. With the change in the coding system from ICD-10 to ICD-11 (Eleventh Revision of the International Classification of Diseases), ACM will no longer be considered as separate entity but will be contained in a broader category of "Cardiomyopathy due to drugs or other external agents" (World Health Organization, 2019a). Thus, with the uptake of the ICD-11 in the near future, civil registry data of ACM will no longer be available, thereby removing the foundation for the method proposed in this dissertation but also removing the foundation of the GBD method.

Anticipating the change in the ICD coding system highlights the need for alternative methods allowing to quantify the contribution of alcohol to CM. To achieve this aim with historical register-based and prospective cohort studies, several barriers need to be overcome. First, many CM remain undiagnosed during lifetime or are falsely classified at death, thus, register-based studies may underestimate the contribution of alcohol to CM. Second, most if not all prospective studies initiated in the past rely on single assessments of alcohol use and lack indicators of chronic heavy drinking over a sustained period of time. Yet, chronic exposure of alcohol consumption for at least five or ten years has been identified as necessary prerequisite which needs further refinement (Guzzo-Merello et al., 2014; Rehm, Hasan, et al., 2017). Third, the feasibility of classic prospective studies (for CVD risk of alcohol use, see e.g. (Millwood et al., 2019)) is severely limited due to the relatively small number of incident cases. For instance, using a nationwide hospital dataset on 8 million discharges in the USA, a recent study identified only about 3,500 or 0.05% cases with ACM (Ram et al., 2018). Consequently, prospective cohort studies would require an overly large sample of participants for studying the link of alcohol consumption and ACM.

In summary, the contribution of alcohol to CM can no longer be estimated using the proposed method in the near future. Given the outlined problems with register-based and prospective cohort studies, case-control studies may emerge as a pragmatic means to study this link. However, to validate results from such studies, it should be examined if patients diagnosed with ACM during lifetime differ from those diagnosed at death only (for first results on this subject, see (Hietanen et al., 2019)). Lastly, the lag time between chronic heavy drinking and development of ACM will also be an important determinant for estimating the burden of disease of ACM. While a 10-year period was proposed in **study III**, future studies linking alcohol consumption and ACM are needed to ascertain the exact interval (for a summary of the challenges in determining the lag time, see **section 6.4.2**).

### 7.3.2 Geographical distribution of alcoholic cardiomyopathy

In **study II**, it was estimated that 3 out of 4 ACM deaths occurred in the Russian Federation. This is not surprising as alcohol consumption in Russia was exceedingly high until early 2000s, peaking at an APC of more than 20 liters pure alcohol in 2003 (The Lancet, 2019). Following the implementation of alcohol control policies, however, alcohol consumption could be substantially reduced, reaching 11.7 liters in 2016 (Neufeld, Ferreira-Borges, & Rehm, 2019). In Russia, parallel to reductions in alcohol consumption between 2005 and 2016, the age-standardized mortality of ACM among males fell from 45 to 22 per 100,000 deaths. While similar reductions could be observed for mortality from alcohol poisonings, alcoholic psychoses, and alcoholic liver diseases, ACM remains the most prevalent alcohol-attributable cause of death in Russia. As alcoholic liver disease is the dominant alcohol-attributable disease in most other countries, this finding points to a very distinct geographical pattern. According to GBD estimates, the ratio of standardized death rates between alcoholic liver disease and ACM was estimated at 5.3 in Western Europe (Germany: 2.7, United Kingdom: 7.9) in 2017. In contrast, there are only five countries globally in which the age-standardized death rates of ACM clearly exceeds those of alcoholic liver disease – all of which were former Soviet or Yugoslavian states: Latvia, Montenegro, Russia, and Ukraine (Institute for Health Metrics and Evaluation, 2019).

Future research should examine commonalities of comparably high ACM mortality rates in Eastern European countries. The relatively high ACM burden in these countries may be driven by drinking patterns, which is characterized by a high proportion of alcohol consumed as spirits on heavy drinking occasions (Shield et al., 2016). In Russia, continuous periods of drunkenness lasting several days ('zapoi') were prevalent among working-age men in the 2000s (Tomkins et al., 2007). Another important driver for high ACM mortality rates in these countries could be differences in issuing death certificates and identifying the underlying cause of death. As shown in **study III**, the vast majority of CM are falsely classified with ill-defined cause of death codes, such as HF. For people dying from sudden cardiac arrest, CM may not be considered as underlying cause if no diagnosis had been given during lifetime - despite the high prevalence of sudden cardiac arrest among patients with dilated CM (Weintraub et al., 2017). In fact, ascertainment of dilated CM involves methods that can only be applied to living persons (e.g. electrocardiogram). For deceased persons, CM may only be identified using more elaborated methods (e.g. cardiac magnetic resonance imaging) which are unlikely to be applied routinely. In some countries of the former Soviet Union, however, autopsies are obligatory for many deceased persons (e.g., Belarus (Kodeksy-by.com, 2017); Kyrgyzstan (Ministry of Justice of the Kyrgyz Republic, 2017); Russia (Leon et al., 2010; Rg.ru, 2017); Ukraine (Prostopravo.com.ua, 2017)), increasing the likelihood to identify enlarged or thickened heart muscles as underlying cause of death. If autopsy findings are combined with indicators of heavy and sustained alcohol use as documented in medical records or reported by friends, colleagues or family members, routinely conducted autopsies may contribute to explain higher rates of ACM in this region.

## 7.4 Implications for alcohol policy

The burden of ACM seems to be largely restricted to a few dozen countries with alcohol consumption clearly above the global average. Thus, measures to reduce ACM burden over and above measures to reduce the burden from alcohol consumption may not be required for many countries (for a summary of the so-called best buys to reduce alcohol consumption, see (World Health Organization, 2018b)). Most countries have already established routine monitoring systems to oversee the progress towards the global goal of a 10% reduction of alcohol use by 2025 relative to 2010 (World Health Organization, 2013). For all countries with recognizable ACM burden, inclusion of ACM mortality rates in such monitoring efforts may facilitate recognition of excessive ACM mortality burden. In most European countries, where declines in alcohol consumption and attributable burden have been observed in recent years (Rehm, Manthey, et al., 2019; World Health Organization, 2018b), ACM mortality rates would be expected to decrease at a steeper pace than APC. Such trends would be expected because ACM is closely linked to heavy consumption levels (Guzzo-Merello et al., 2014) and similar observations were made for alcohol poisonings in Russia (Nemtsov, Neufeld, & Rehm, 2019). In countries with diverging patterns (e.g. increases in ACM rates despite falling consumption) or with increases in alcohol consumption (e.g. in India, Myanmar, or Vietnam (Manthey et al., 2019)), alcohol policy measures may be considered to reverse these trends. For this purpose, any intervention targeting the prerequisite behavior, i.e. chronic heavy alcohol use over an extended period of time, might be a viable option.

One such measure aiming to reduce alcohol consumption among heavy drinkers is 'minimum unit pricing', i.e. setting a floor price based on alcohol content and resulting in retail price increases for cheap alcoholic beverages. Following the introduction of this policy on 1 May 2018 in Scotland, alcohol purchases decreased only in those households purchasing the largest alcohol volumes (O'Donnell et al., 2019), suggesting this measure as viable option to reduce heavy alcohol use. In Russia, a floor price for vodka was introduced in 2003 – however an evaluation of this specific policy measure, including effects on ACM, has not been conducted to date (Neufeld, Ferreira-Borges, et al., 2019). While efforts to increase retail prices are generally found to be highly cost-effective in reducing alcohol consumption and attributable burden (Chisholm et al., 2018), they may in turn also incentivize consumption of unrecorded alcohol, e.g. surrogate, illegally manufactured, home-brewed, or imported alcohol (Neufeld, Wittchen, Ross, Ferreira-Borges, & Rehm, 2019). It should further be taken into account that unrecorded alcohol has some additional risks (Lachenmeier & Rehm, 2009; Rehm, Kailasapillai, et al., 2014) and is most prevalent among heavier drinkers (Manthey et al., 2020) – the primary risk group for ACM. Thus, increases in unrecorded alcohol consumption may attenuate or even offset the intended effects of pricing policies. In light of the available evidence, raising retail prices of alcoholic beverages may be tentatively recommended to reduce heavy drinking and consequently ACM burden.

## 7.5 Outlook

This dissertation comprehensively describes the epidemiology of ACM mortality, highlighting the need for high-quality civil registry mortality data. Beginning in early 2019 (World Health Organization, 2019b), the transition from ICD-10 to ICD-11 will have some important implications for cause of death coding. Most importantly, the so-called cluster coding is thought to replace the single coding as schemed by the ICD-10. Specifically, the ICD-11 will require physicians to combine all contributing information of a disease, rather than assigning a single diagnosis which already contains all relevant information by definition (Eckert & Vogel, 2018). This way, ICD-11 diagnoses are expected to contain a larger array of information, with many benefits for monitoring population health. While causal drivers such as alcohol use would need to be captured in cluster codes, it presupposes 1) that physicians are aware of the patients' drinking patterns and 2) that physicians are willing to document alcohol use in their diagnoses. However, as discussed above, patients' alcohol use is a topic barely talked about by physicians and moreover is often neglected in death certificates (see section **7.2.3**). Thus, unless alcohol use is recognized as important risk factor and dealt with routinely by medical professionals, changes in the coding system will hardly increase the number of ACM cases correctly identified by physicians.

Irrespective of the prevailing coding system, the quality of mortality statistics is constantly changing for the better. Take for instance Germany, where the use of CVD garbage codes has declined between 2000 and 2016 (Stolpe & Stang, 2019) and where an increasing number of handwritten death certificates are processed using electronic coding systems, thereby increasing accuracy in determining the underlying cause of death by adhering to international standards (Eckert, 2019). In fact, increasing use of modern technology in health care may also pave the way to include multiple-cause data in mortality statistics. As alcohol is often falsely classified as contributing but not underlying cause of death (Daula & Hanzlick, 2006), multiple cause of death data may be used to correct for some degree of underreporting of alcohol-attributable diseases (for correcting mortality underestimates of dementia, see (Buschner & Grunwald-Muhlberger, 2019)), but likely not all of it (Pollock et al., 1987). For global mortality monitoring, and for ACM in particular, data availability and quality in the most populous countries India and China will be crucial. In India – one of those countries with largest increases in alcohol consumption globally (Manthey et al., 2019) – coverage of registered deaths has risen from 52 to 67% in 2010 (Mikkelsen et al., 2015). Further, verbal autopsies (i.e., structured interviews to assess the underlying cause of death) have been established as viable supplement to civil registry systems in low- and middle-income countries (World Health Organization, 2016b). On this basis, initiatives such as India's Million Death's Study have provided detailed information on unregistered deaths (Gomes et al., 2017), shaping what we know about disease burden in this country (Dandona et al., 2017). In summary, a greater coverage of registered deaths and enhanced quality of available mortality statistics can be anticipated, laying the foundation for refined global ACM mortality estimates in the future.

## 7.6 Conclusion

In the first study, methods for estimating the global contribution of alcohol consumption to mortality from CM were developed using data from 50 countries with civil registries. For the first time, feasibility of estimating ACM mortality was demonstrated and the proposed methods were later adopted by the WHO in estimating the global alcohol-attributable disease burden.

In the second study, about 26,000 deaths were estimated to be attributable to ACM in 2015, globally. In other words, every 15$^{th}$ death from CM could be fully avoided if chronic heavy drinking patterns were non-existent. Geographical variation of ACM mortality was more skewed than found for other alcohol-attributable conditions, with 76% of all ACM deaths being estimated to occur in Russia alone. However, in nearly half of all countries with civil registry data, a substantial number of ACM deaths was found to be likely misclassified as other cause of death.

The last study quantified the degree of ACM underreporting in civil registries and revealed the importance of ill-defined cause of death codes for ACM mortality estimates. For every registered ACM death, up to 6 ACM deaths may be misclassified with ill-defined codes. While the redistribution of ill-defined cause of death codes is required to compare mortality estimates over time and across locations, the work identified that current redistribution algorithms are not aligned with population alcohol exposure, resulting in implausible high ACM mortality estimates in the elderly.

In conclusion, this dissertation provides a first and comprehensive assessment of the global epidemiology of ACM mortality based on civil registry mortality data. Further, barriers and facilitators for estimating ACM mortality globally are identified and discussed. The ACM mortality estimates presented in this project are likely underestimates as the underlying approach does not account for misclassified ACM deaths. However, alternative ACM mortality estimates taking these limitations into account are likely overestimates. Finally, after full transition to ICD-11, new methods to estimate ACM mortality will be required as civil registry data will cease to provide the foundation for the methods proposed in this dissertation.

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# 9 Appendix A (study I)

The following additional files were published together with the study (for access: https://pophealthmetrics.biomedcentral.com/articles/10.1186/s12963-017-0137-1):

**Additional file A.1:** ACM Quantification_GATHER checklist. (DOCX 17 kb)

**Additional file A.2:** Stata file (DTA 89 kb)

**Additional file A.3:** Syntaxes (ZIP 8 kb)

**Additional file A.4:** Results from all four models including model data (XLSX 365 kb)

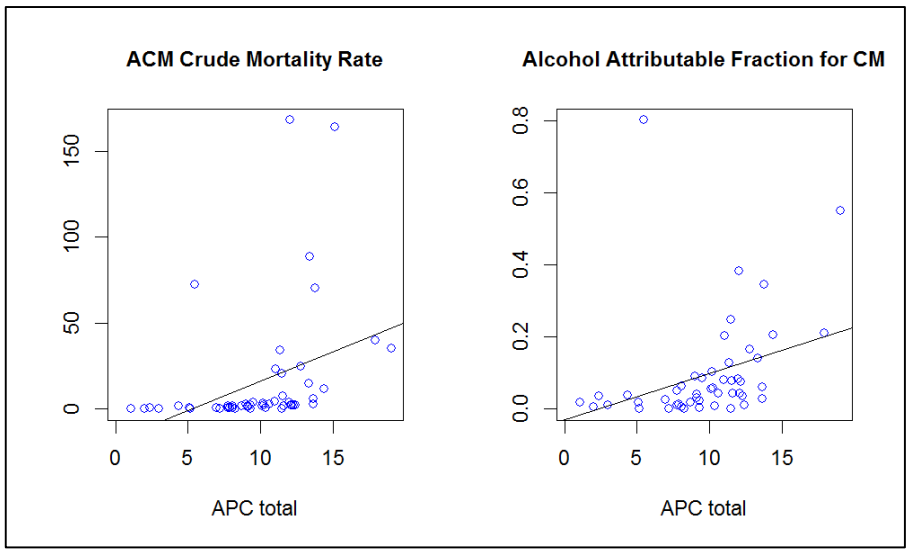


**Figure A.1** Scatterplot and regression line of total alcohol per capita (APC) with crude mortality rate and alcohol attributable fractions

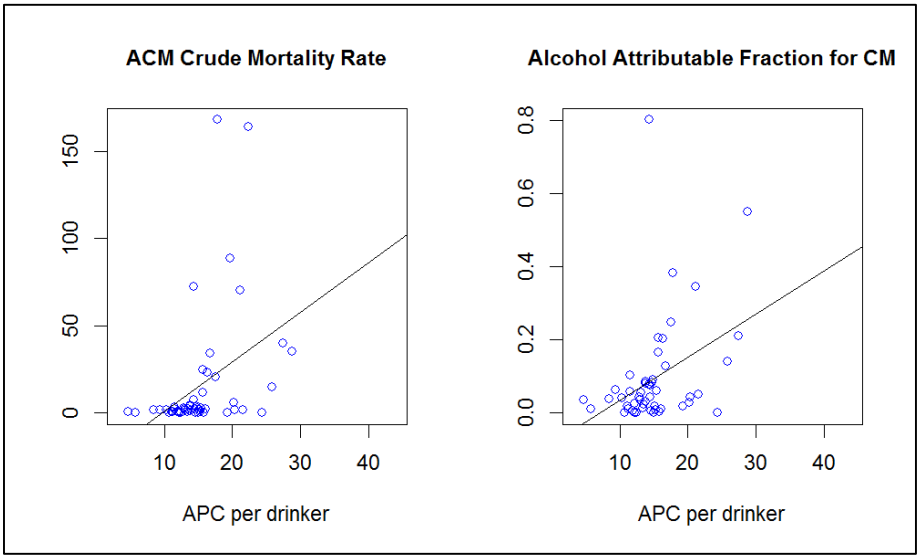


**Figure A.2** Scatterplot and regression line of alcohol per capita (APC) per drinker with crude mortality rate and alcohol attributable fractions

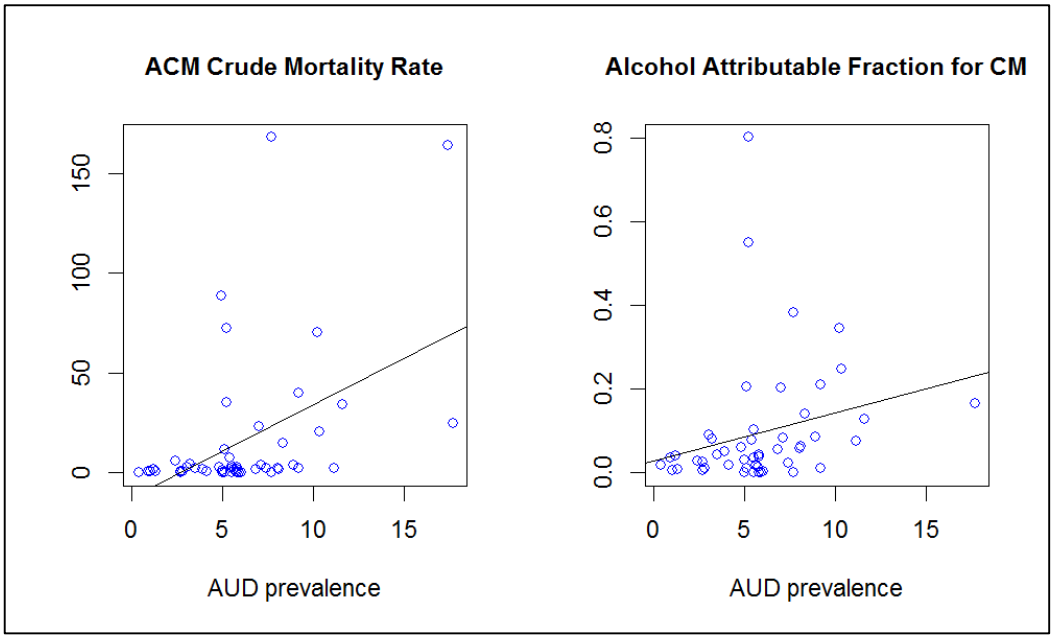


**Figure A.3** Scatterplot and regression line of alcohol use disorder (AUD) prevalence with crude mortality rate and alcohol attributable fractions

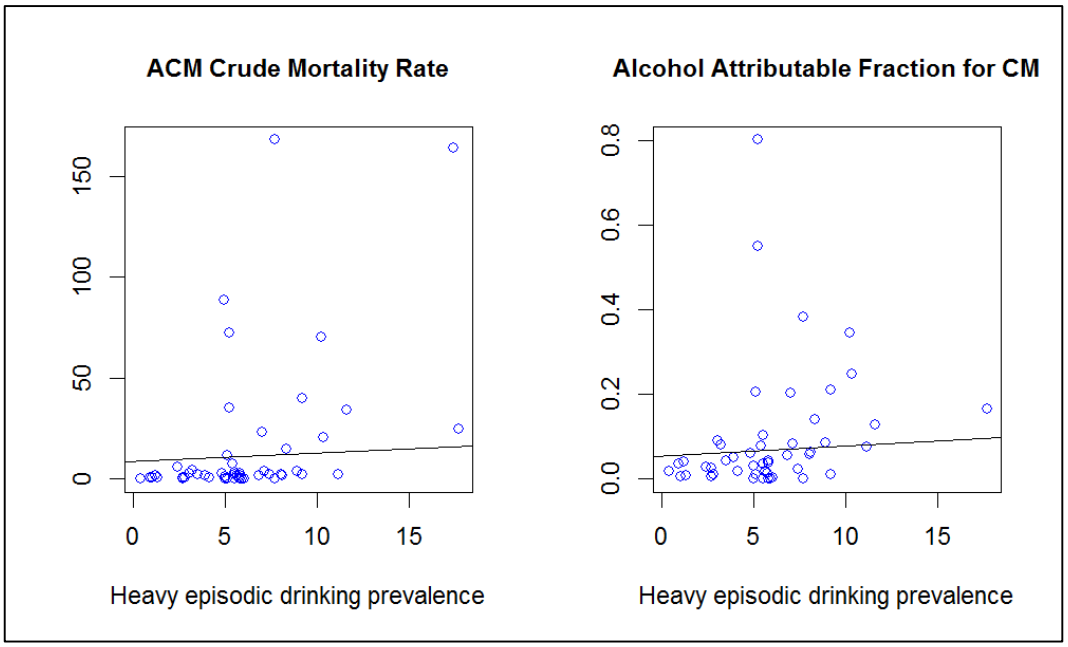


**Figure A.4** Scatterplot and regression line of heavy episodic drinking prevalence with crude mortality rate and alcohol attributable fractions

# 10 Appendix B (study II)

## 10.1 Methods

The methods are largely based on a previous publication (Manthey et al., 2017). This document gives a detailed description on the modelling decisions for the current analysis.

### 10.1.1 Mortality data

As alcohol exposure is traditionally measured for populations 15 and older (Poznyak et al., 2013; World Health Organization, 2017b), all mortality data was restricted to this age group.

Data on deaths due to ACM were mainly retrieved from the WHO mortality data base (World Health Organization, 2017c). Where any three-digit ICD-10 I42.X code was reported, we obtained the sex- and age-specific number of ACM (ICD-10 code I42.6) deaths for the three most recent years. If no ICD-10 I42.6 death was reported, 0 ACM deaths were coded. For *N*=89 WHO member states, sex-specific mortality data could be obtained from this data base. For Russia and Slovenia, ACM mortality figures were obtained by government sources ((Federal State Statistics Service (Rosstat), 2015; Barbara Lovrečič, Lovrečič, & Simonović, 2016)).

For more stability in ACM mortality data, three-year moving averages were used where available (*N*=5 countries with data from one year, *N*=3 from two years, *N*=83 from three years). The obtained ACM mortality data were recorded between 1995 and 2016 (median = 2014). For the majority of countries (*N*=79), at least one source year was in the most current three-year-period of available mortality data (2013-2015), whereas for 14 countries all mortality data were recorded before 2013.

In all countries without ACM mortality data (*N*=102), all covariate data was based on 2015 values.

All data on deaths due to CM were sourced from the WHO (World Health Organization, 2017a). These figures represent all deaths due to “Cardiomyopathy, myocarditis, endocarditis”. To allow for comparisons with ACM mortality data from the GBD study, country-specific data were obtained from the GBD Results Tool (Institute for Health Metrics and Evaluation, 2017).

### 10.1.2 Covariate data

The most recent estimates for APC from 2015 or earlier were obtained from the Global Information System on Alcohol and Health (World Health Organization, 2017b).

The proportion of people with AUD and the proportion of current drinker was obtained from the Global Status Report on Alcohol and Health (World Health Organization, 2014). For a small number of countries without data, we assumed the same proportions of AUD and current drinker as the nearest countries with available data (Cook Islands, Marshall Islands, Niue, Nauru, Palau, Tuvalu = Federated States of Micronesia; Monaco = France; Saint Kitts and Nevis = Antigua and Barbuda; San Marino = Italy).

Population data was sourced from the United Nations World Population Prospects (Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, 2015). Regional clusters were defined as GBD sub regions (Institute for Health Metrics and Evaluation, 2015).

### 10.1.3 Data analyses

It was aimed to model the relationship between population alcohol exposure and deaths due to ACM. In an extensive process, potential sex-specific candidate models were reviewed for best data fit. First, non-nested candidate models were built using APC, AUD prevalence and number of CM deaths as predictors. Poisson and negative binomial models were considered to be adequate regression techniques as the majority of countries reported very few or zero deaths (Hilbe, 2014). Likelihood ratio tests indicated best fit of negative binomial models. Due to excess zeroes in the outcome variable, an additional zero-inflation term was considered to improve the model. Vuong tests indicated best fit for non-inflated models. Subsequently, a number of candidate models using various combinations of potential covariates (AUD, APC, proportion of drinkers, population size, number of CM deaths) were reviewed referring to density plots, comparison of observed and fitted values, and plausibility of predictions (e.g. fewer ACM deaths than CM deaths). Finally, for well-fitting models, likelihood ratio and Vuong tests evaluated if alternative model specifications (i.e., Poisson and/or zero-inflation) can improve data fit. In **Table B.1** and **Table B.2**, model specifications of key candidate models including results from likelihood ratio and Voung tests are presented for the female and male population, respectively.

Eventually, two negative binomial regression models were selected. In the female model, ACM deaths were predicted by APC among females (Incidence rate ratio (IRR) = 1.72, 95% CI: 1.20-2.62, $p$<.001), AUD prevalence (IRR = 1.18, 95% CI: 0.82-1.75, $p$=.323), the log population size (IRR = 0.66, 95% CI: 0.48-0.93, $p$=.001), in addition to using the log of CM deaths as offset. In the male model, ACM deaths were predicted by APC among males (IRR = 1.23, 95% CI: 1.15-1.30, $p$<.001) and the log of CM deaths (IRR = 2.30, 95% CI: 1.91-2.84, $p$<.001).

In order to evaluate the goodness of fit of the models, we looked at residuals-vs-fitted plots and density plots of predicted vs. recorded values for visual inspection. Further, we compared predicted and recorded values, where absolute differences of at least 10 deaths per 1,000,000 adults and of 5% in the AAF were identified as relevant deviations. Systematic differences in the regional distributions (using standardized residuals larger than 1.96) were identified between countries within and beyond these thresholds.

In *N*=3 countries (Niue, Nauru, Tuvalu) 0 CM deaths were recorded for females and males. As this implies 0 ACM deaths counts, they were excluded from the models.

A newly computed variable contained the number of recorded ACM deaths and added predicted deaths for countries without any recorded mortality data. 95% CI were obtained from the predicted standard error for both recorded and predicted values. Thus, this variable presented the main results, denoting ACM mortality data for each country by sex. Mortality rates (expressed as number of ACM deaths per 1,000,000 adults) and AAF were calculated from this variable.

A combination of sex-stratified results produced figures for the total population. ACM deaths were summed up over sex, the mortality rates were weighted using female and male population sizes, and the AAF were weighted using the sex-specific number of CM deaths. Aggregation over countries was done in an analogous manner.

In the additional analysis, countries with underreporting ACM deaths were identified as countries in which the recorded number of ACM deaths was lower than the rounded lower CI of the corresponding predicted number of ACM deaths. This was done separately by sex and for the total population. As quantitative indicator for underreporting, the difference between predicted and recorded ACM deaths was summed over the identified countries. All analyses were performed with R (R Core Team, 2016).

**Table B.1** Female candidate model coefficients and selection details

| | Alcohol per capita (APC) | Alcohol use disorder (AUD) | log(population size) | Zero-inflation term: APC | Zero-inflation term: AUD | Akaike's information criterion (AIC) | Likelihood ratio test* | AIC-corrected Vuong test** |
|---|---|---|---|---|---|---|---|---|
| Negative binomial model (final model) | 0.54 (0.18-0.96) | 0.17 (-0.20-0.56) | -0.42 (-0.72- -0.07) | | | 399.12 | *p*<.001 | |
| Poisson model | 0.78 (0.70-0.86) | 0.69 (0.66-0.72) | -0.11 (-0.15- -0.07) | | | 2035.13 | | |
| Zero-inflated negative binomial model | 0.11 (-0.27-0.48) | 0.28 (-0.08-0.63) | -0.45 (-0.81- -0.08) | -2.62 (-5.09- -0.16) | 0.39 (-0.72-1.5) | 389.69 | | *p*=0.160 |

Note: * Likelihood ratio test evaluated superiority of negative binomial over Poisson model; ** Vuong test examined superiority of zero-inflated negative binomial over non-inflated negative binomial model

**Table B.2** Male candidate model coefficients and selection details

| | Alcohol per capita (APC) | log(number of cardiomyopathy deaths) | Zero-inflation term: APC | Akaike's information criterion (AIC) | Likelihood ratio test* | AIC-corrected Vuong test** |
|---|---|---|---|---|---|---|
| Negative binomial model (final model) | 0.20 (0.14-0.26) | 0.83 (0.65-1.04) | | 605.56 | *p*<.001 | |
| Poisson model | 0.25 (0.24-0.25) | 1.05 (1.03-1.06) | | 4373.44 | | |
| Zero-inflated negative binomial model | 0.18 (0.12-0.24) | 0.86 (0.66-1.05) | -38.76 (-184.41- 106.89) | 603.14 | | *p*=0.229 |

Note: * Likelihood ratio test evaluated superiority of negative binomial over Poisson model; ** Vuong test examined superiority of zero-inflated negative binomial over non-inflated negative binomial model

## 10.2 Results

See **Table B.3** for ACM deaths, mortality rates and AAF for each country by sex.

### 10.2.1 Goodness of fit

For a comparison of recorded and predicted values for each country, see **Table B.4**. In **Figure B.1**, density distribution of recorded and predicted deaths due to ACM are presented by sex and for the total population.

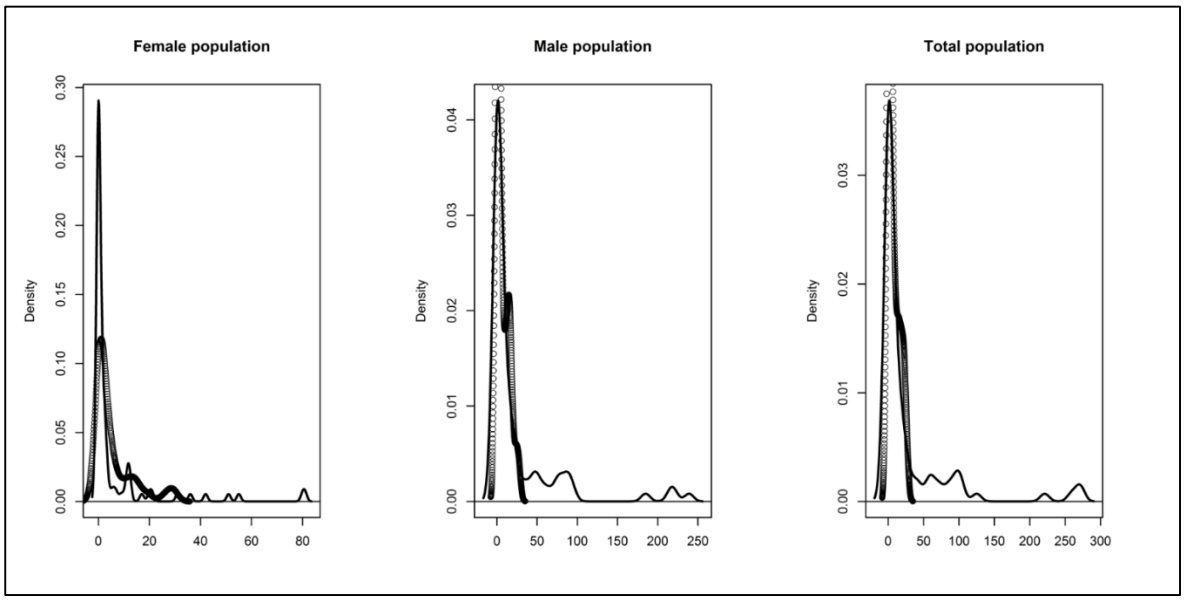


**Figure B.1** Density distribution of alcoholic cardiomyopathy deaths, by sex and total population; Note: Solid lines denote recorded deaths, circles denote predicted deaths

With regard to mortality rates in the total population, relevant deviations were observed in 17 countries (female population: *N*=10, male population: *N*=20). A larger number of countries showed relevant deviations between recorded and predicted AAF (total population: *N*=30, female population: *N*=20, male population: *N*=34). Looking at the comparison of recorded and predicted mortality rates in the total population, a significant number of deviations were found in countries from Central Europe and Eastern Europe (female: Central Europe and Eastern Europe, male: Central Europe and Eastern Europe). Regarding AAF, a significant number of deviations were found in countries from Central Asia, Central Europe, and Eastern Europe (female: Eastern Europe, male: Central Europe, and Eastern Europe). In other words, the majority of regions were not affected by systematic deviation between recorded and predicted values. However, some countries in Central Asia, Central Europe, and Eastern Europe could not be adequately represented by the models (see Table B.4).

### 10.2.2 Additional analyses

Comparing predicted and recorded ACM data results in a set of potentially underreporting countries, which are highlighted in **Table B.4**. For *N*=44 out of 91 countries, underreporting of ACM mortalitly data is probable according to the results of the prediction models.

**Table B.5** contains the vital statistics or modelled ACM mortality and estimates from the GBD study. Comparisons were feasible for 185 countries. For 13 countries highlighted in the Table, GBD estimates were below vital statistics/modelled data. For the remaining countries, GBD estimates exceeded vital statistics/modelled data by 0.1 to 26,800 deaths (mean difference: 326.0, median difference: 20.8).

**Table B.3** Country- and sex-specific distribution of alcoholic cardiomyopathy deaths, mortality rates, and alcohol-attributable fractions

| Country | Number of ACM deaths | | | Mortality rate | | | Alcohol-attributable fraction | | |
|---|---|---|---|---|---|---|---|---|---|
| | total | female | male | total | female | male | total | female | male |
| Afghanistan | 2 (1-6) | 1 (0-3) | 1 (0-3) | 0.1 (0-0.3) | 0.1 (0-0.3) | 0.1 (0.1-0.3) | 0.2% (0.1-0.5%) | 0.1% (0-0.5%) | 0.2% (0.1-0.5%) |
| Albania | 12 (8-18) | 4 (2-8) | 8 (6-11) | 5 (3.3-7.8) | 3.5 (1.9-6.4) | 6.7 (4.7-9.4) | 2% (1.3-3.1%) | 1.5% (0.8-2.7%) | 2.4% (1.7-3.4%) |
| Algeria | 7 (3-19) | 2 (1-7) | 5 (2-12) | 0.2 (0.1-0.7) | 0.1 (0-0.5) | 0.3 (0.1-0.8) | 0.2% (0.1-0.5%) | 0.1% (0-0.4%) | 0.2% (0.1-0.6%) |
| Andorra | 2 (0-5) | 1 (0-3) | 1 (0-2) | 26.6 (7.5-79.7) | 31.6 (7-101.2) | 21.4 (7.9-57.8) | 26% (7.3-78.1%) | 31.3% (7-100%) | 20.8% (7.7-56.2%) |
| Angola | 25 (16-40) | 7 (4-13) | 18 (13-27) | 1.9 (1.2-3.1) | 1 (0.5-2) | 2.9 (2-4.2) | 1.5% (0.9-2.3%) | 0.8% (0.4-1.5%) | 2.3% (1.5-3.3%) |
| Antigua and Barbuda | 0 (0-0) | 0 (0-0) | 0 (0-0) | 0 (0-7.6) | 0 (0-10.8) | 0 (0-4) | 0% (0-17.4%) | 0% (0-19.7%) | 0% (0-12.8%) |
| Argentina | 8 (0-94) | 0 (0-30) | 8 (0-64) | 0.3 (0-3) | 0 (0-1.8) | 0.5 (0-4.2) | 0.1% (0-1.7%) | 0% (0-1.1%) | 0.3% (0-2.4%) |
| Armenia | 1 (1-2) | 0 (0-1) | 1 (1-2) | 0.6 (0.3-1) | 0.2 (0.1-0.5) | 1 (0.6-1.6) | 1.9% (1.1-3.3%) | 0.9% (0.5-1.9%) | 2.8% (1.7-4.7%) |
| Australia | 58 (35-96) | 7 (0-22) | 51 (35-73) | 3 (1.8-5) | 0.7 (0-2.3) | 5.3 (3.7-7.7) | 4.1% (2.5-6.8%) | 1.3% (0-4.1%) | 5.9% (4.1-8.6%) |
| Austria | 12 (0-192) | 2 (0-141) | 10 (0-51) | 1.6 (0-26.2) | 0.5 (0-37.5) | 2.8 (0-14.3) | 0.9% (0-13.8%) | 0.3% (0-18.8%) | 1.5% (0-7.9%) |
| Azerbaijan | 2 (1-4) | 0 (0-1) | 2 (1-3) | 0.3 (0.2-0.5) | 0.1 (0-0.2) | 0.5 (0.3-0.9) | 0.6% (0.3-1.2%) | 0.4% (0.2-0.9%) | 0.7% (0.4-1.3%) |
| Bahamas | 0 (0-1) | 0 (0-1) | 0 (0-0) | 0 (0-4) | 0 (0-5.2) | 0 (0-2.7) | 0% (0-3%) | 0% (0-5.3%) | 0% (0-1.6%) |
| Bahrain | 0 (0-1) | 0 (0-0) | 0 (0-0) | 0.3 (0.1-0.6) | 0.3 (0.1-0.9) | 0.3 (0.1-0.5) | 0.6% (0.3-1.5%) | 0.6% (0.2-2%) | 0.6% (0.3-1.3%) |
| Bangladesh | 1 (0-3) | 0 (0-1) | 1 (0-2) | 0 (0-0) | 0 (0-0) | 0 (0-0) | 0.1% (0.1-0.4%) | 0.1% (0-0.3%) | 0.2% (0.1-0.5%) |
| Barbados | 0 (0-3) | 0 (0-1) | 0 (0-1) | 0 (0-11.5) | 0 (0-11.5) | 0 (0-11.6) | 0% (0-7.1%) | 0% (0-10.6%) | 0% (0-5.2%) |
| Belarus | 403 (215-770) | 29 (9-91) | 374 (206-679) | 50.5 (27-96.6) | 6.7 (2.1-20.9) | 103 (56.7-187.1) | 20.2% (10.8-38.5%) | 5.9% (1.9-18.4%) | 24.8% (13.7-45.1%) |
| Belgium | 23 (0-76) | 3 (0-33) | 20 (5-42) | 2.5 (0-8.1) | 0.6 (0-7) | 4.4 (1.1-9.3) | 2.2% (0-7.3%) | 0.5% (0-6%) | 4.2% (1-8.8%) |
| Belize | 0 (0-1) | 0 (0-0) | 0 (0-0) | 0 (0-3.4) | 0 (0-2.7) | 0 (0-4.2) | 0% (0-4.5%) | 0% (0-6.3%) | 0% (0-3.8%) |
| Benin | 2 (1-4) | 1 (0-2) | 1 (1-2) | 0.3 (0.2-0.7) | 0.3 (0.1-0.6) | 0.4 (0.2-0.7) | 0.6% (0.3-1.1%) | 0.4% (0.2-1%) | 0.7% (0.4-1.3%) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Bhutan | 0 (0-0) | 0 (0-0) | 0 (0-0) | 0.2 (0.1-0.5) | 0.2 (0.1-0.8) | 0.1 (0-0.3) | 0.6% (0.2-1.9%) | 0.7% (0.2-2.3%) | 0.5% (0.2-1.3%) |
| Bolivia (Plurinational State of) | 0 (0-5) | 0 (0-3) | 0 (0-2) | 0 (0-0.9) | 0 (0-1.1) | 0 (0-0.7) | 0% (0-0.7%) | 0% (0-0.9%) | 0% (0-0.5%) |
| Bosnia and Herzegovina | 51 (29-88) | 26 (14-49) | 24 (15-40) | 15.4 (8.9-26.8) | 15.8 (8.6-29.2) | 15 (9.3-24.4) | 1.3% (0.7-2.2%) | 1.1% (0.6-2%) | 1.5% (0.9-2.5%) |
| Botswana | 5 (3-8) | 1 (1-2) | 4 (2-6) | 3.3 (2-5.4) | 1.6 (0.8-3.2) | 5 (3.2-7.7) | 3.6% (2.2-6%) | 1.7% (0.8-3.4%) | 5.7% (3.7-8.8%) |
| Brazil | 259 (112-561) | 20 (2-70) | 239 (111-490) | 1.6 (0.7-3.6) | 0.2 (0-0.9) | 3.1 (1.4-6.4) | 1.4% (0.6-3.1%) | 0.3% (0-0.9%) | 2.2% (1-4.6%) |
| Brunei Darussalam | 0 (0-0) | 0 (0-0) | 0 (0-0) | 0.3 (0.1-1) | 0.3 (0.1-1.2) | 0.3 (0.1-0.8) | 0.6% (0.2-1.8%) | 0.9% (0.2-3.1%) | 0.5% (0.2-1.1%) |
| Bulgaria | 8 (0-113) | 0 (0-42) | 8 (0-71) | 1.3 (0-18.2) | 0 (0-13.1) | 2.7 (0-23.8) | 0.3% (0-4.4%) | 0% (0-2.9%) | 0.7% (0-6.2%) |
| Burkina Faso | 18 (12-28) | 3 (1-7) | 15 (11-20) | 1.8 (1.2-2.8) | 0.6 (0.2-1.5) | 3.1 (2.3-4.2) | 2.2% (1.5-3.4%) | 0.7% (0.3-1.8%) | 3.9% (2.8-5.2%) |
| Burundi | 8 (6-12) | 2 (1-3) | 7 (5-10) | 1.4 (0.9-2) | 0.5 (0.3-0.9) | 2.3 (1.6-3.2) | 2.3% (1.6-3.4%) | 0.9% (0.5-1.6%) | 3.5% (2.5-4.9%) |
| Cabo Verde | 0 (0-1) | 0 (0-0) | 0 (0-0) | 1 (0.4-2.3) | 0.7 (0.3-1.8) | 1.3 (0.6-2.8) | 2.8% (1.2-6.5%) | 2.2% (0.8-5.8%) | 3.3% (1.6-7.1%) |
| Cambodia | 8 (5-12) | 2 (1-4) | 6 (4-8) | 0.7 (0.5-1.1) | 0.3 (0.2-0.7) | 1.1 (0.8-1.6) | 1.3% (0.9-2%) | 0.6% (0.3-1.1%) | 2.3% (1.6-3.3%) |
| Cameroon | 29 (21-42) | 4 (2-7) | 25 (18-34) | 2.2 (1.5-3.1) | 0.6 (0.4-1.1) | 3.8 (2.8-5.2) | 2.9% (2.1-4.2%) | 1% (0.5-1.7%) | 4.4% (3.2-6%) |
| Canada | 59 (42-86) | 12 (7-23) | 47 (36-63) | 2 (1.4-2.9) | 0.8 (0.5-1.5) | 3.3 (2.5-4.4) | 4% (2.9-5.8%) | 1.9% (1.1-3.6%) | 5.5% (4.1-7.3%) |
| Central African Republic | 2 (1-4) | 1 (0-2) | 1 (1-2) | 0.6 (0.3-1.2) | 0.5 (0.2-1.1) | 0.8 (0.4-1.3) | 0.7% (0.4-1.4%) | 0.5% (0.2-1.3%) | 0.8% (0.5-1.5%) |
| Chad | 2 (1-4) | 0 (0-2) | 1 (0-2) | 0.2 (0.1-0.5) | 0.1 (0-0.4) | 0.3 (0.1-0.6) | 0.3% (0.1-0.8%) | 0.2% (0.1-0.7%) | 0.4% (0.2-0.8%) |
| Chile | 13 (5-25) | 1 (0-5) | 12 (6-20) | 0.9 (0.4-1.7) | 0.1 (0-0.6) | 1.7 (0.9-2.9) | 1.6% (0.7-3.1%) | 0.3% (0-1.6%) | 2.4% (1.2-4%) |
| China | 237 (102-577) | 19 (4-91) | 218 (98-485) | 0.2 (0.1-0.5) | 0 (0-0.2) | 0.4 (0.2-0.8) | 0.6% (0.3-1.6%) | 0.1% (0-0.5%) | 1.3% (0.6-2.8%) |
| Colombia | 0 (0-10) | 0 (0-4) | 0 (0-6) | 0 (0-0.3) | 0 (0-0.2) | 0 (0-0.4) | 0% (0-0.7%) | 0% (0-0.6%) | 0% (0-0.8%) |
| Comoros | 0 (0-0) | 0 (0-0) | 0 (0-0) | 0.4 (0.1-1.1) | 0.4 (0.1-1.5) | 0.4 (0.2-0.8) | 0.6% (0.2-1.8%) | 0.7% (0.2-2.5%) | 0.5% (0.2-1.2%) |
| Congo | 5 (3-9) | 1 (0-3) | 4 (3-6) | 1.9 (1.2-3.3) | 1 (0.4-2.4) | 2.9 (1.9-4.2) | 2.7% (1.6-4.6%) | 1.4% (0.6-3.5%) | 3.9% (2.6-5.7%) |
| Cook Islands | 0 (0-1) | 0 (0-1) | 0 (0-0) | 16.7 (4.2-72.5) | 17.2 (3.1-95.5) | 16.2 (5.3-49.1) | 11.3% (2.9-49.1%) | 11.8% (2.1-65.2%) | 10.9% (3.6-32.9%) |
| Costa Rica | 5 (4-7) | 0 (0-1) | 5 (4-6) | 1.4 (1.1-2) | 0 (0-0.6) | 2.8 (2.4-3.4) | 1.9% (1.5-2.8%) | 0% (0-1%) | 3.2% (2.8-4%) |
| Cote d'Ivoire | 28 (19-42) | 6 (3-11) | 23 (16-32) | 2.2 (1.5-3.2) | 0.9 (0.5-1.7) | 3.4 (2.4-4.7) | 2.4% (1.6-3.5%) | 1.1% (0.6-2%) | 3.4% (2.5-4.7%) |
| Croatia | 39 (32-50) | 6 (4-9) | 33 (28-41) | 10.8 (8.9-13.7) | 3.2 (2.3-4.7) | 19.1 (16.1-23.6) | 11.3% (9.3-14.4%) | 4.5% (3.3-6.8%) | 15.5% (13-19.1%) |
| Cuba | 84 (80-91) | 5 (4-7) | 79 (76-83) | 8.8 (8.4-9.5) | 1.1 (0.8-1.5) | 16.6 (16-17.6) | 10.3% (9.8-11.1%) | 1.8% (1.4-2.7%) | 14.5% (14-15.3%) |
| Cyprus | 1 (0-5) | 0 (0-2) | 1 (0-3) | 1 (0-5.5) | 0 (0-4.2) | 2 (0-6.8) | 1.8% (0-9.3%) | 0% (0-8.3%) | 3% (0-10.1%) |
| Czechia | 24 (0-127) | 3 (0-29) | 21 (0-98) | 2.7 (0-14.1) | 0.7 (0-6.3) | 4.8 (0-22.4) | 3.8% (0-20.3%) | 1.6% (0-15.1%) | 4.8% (0-22.6%) |
| Democratic People's Republic of Korea | 5 (2-9) | 1 (0-3) | 4 (2-6) | 0.2 (0.1-0.4) | 0.1 (0-0.3) | 0.4 (0.2-0.6) | 0.6% (0.3-1.1%) | 0.3% (0.1-0.7%) | 0.8% (0.5-1.4%) |
| Democratic Republic of the Congo | 8 (4-18) | 2 (1-7) | 6 (3-11) | 0.2 (0.1-0.4) | 0.1 (0-0.3) | 0.3 (0.1-0.6) | 0.3% (0.1-0.7%) | 0.2% (0.1-0.5%) | 0.5% (0.2-0.9%) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Denmark | 6 (0-14) | 2 (0-5) | 4 (0-9) | 1.3 (0.1-3.1) | 0.8 (0-2.3) | 1.7 (0.2-4) | 2.3% (0.2-5.6%) | 2.1% (0.1-5.7%) | 2.4% (0.3-5.5%) |
| Djibouti | 0 (0-1) | 0 (0-0) | 0 (0-0) | 0.3 (0.1-1) | 0.4 (0.1-1.3) | 0.3 (0.1-0.7) | 0.5% (0.2-1.4%) | 0.6% (0.2-2%) | 0.4% (0.2-0.9%) |
| Dominica | 0 (0-2) | 0 (0-2) | 0 (0-0) | 0 (0-39.8) | 0 (0-59) | 0 (0-20.3) | 0% (0-14.3%) | 0% (0-26.7%) | 0% (0-6%) |
| Dominican Republic | 1 (0-5) | 0 (0-2) | 1 (0-3) | 0.1 (0-0.7) | 0 (0-0.5) | 0.3 (0-0.8) | 0.3% (0-1.4%) | 0% (0-0.9%) | 0.8% (0-2%) |
| Ecuador | 2 (0-5) | 1 (0-2) | 1 (0-3) | 0.2 (0-0.4) | 0.2 (0.1-0.4) | 0.2 (0-0.5) | 0.6% (0.1-1.3%) | 0.7% (0.4-1.5%) | 0.5% (0-1.2%) |
| Egypt | 18 (6-57) | 7 (2-25) | 11 (4-32) | 0.3 (0.1-0.9) | 0.2 (0.1-0.8) | 0.4 (0.1-1) | 0.1% (0-0.4%) | 0.1% (0-0.3%) | 0.2% (0.1-0.5%) |
| El Salvador | 0 (0-1) | 0 (0-0) | 0 (0-1) | 0 (0-0.3) | 0 (0-0.2) | 0 (0-0.3) | 0% (0-0.8%) | 0% (0-1%) | 0% (0-0.7%) |
| Equatorial Guinea | 6 (3-14) | 2 (1-7) | 4 (2-7) | 12.3 (5.7-28) | 10 (3.3-30.1) | 14.4 (8-26) | 10.9% (5.1-24.8%) | 9.9% (3.3-29.8%) | 11.6% (6.4-21%) |
| Eritrea | 1 (0-1) | 0 (0-1) | 0 (0-1) | 0.2 (0.1-0.5) | 0.2 (0.1-0.4) | 0.2 (0.1-0.5) | 0.4% (0.2-1%) | 0.4% (0.1-1%) | 0.5% (0.2-0.9%) |
| Estonia | 73 (44-128) | 9 (6-16) | 64 (38-112) | 65.3 (39.4-114.5) | 14.9 (9.6-26.4) | 125 (74.7-218.7) | 30.7% (18.5-53.8%) | 15.3% (9.9-27.1%) | 35.8% (21.4-62.6%) |
| Ethiopia | 10 (4-21) | 2 (0-5) | 8 (4-16) | 0.2 (0.1-0.4) | 0.1 (0-0.2) | 0.3 (0.1-0.6) | 0.3% (0.2-0.7%) | 0.1% (0-0.4%) | 0.5% (0.2-1%) |
| Fiji | 0 (0-1) | 0 (0-1) | 0 (0-0) | 0 (0-1.9) | 0 (0-2.6) | 0 (0-1.3) | 0% (0-1.2%) | 0% (0-1.8%) | 0% (0-0.8%) |
| Finland | 88 (74-110) | 12 (8-19) | 76 (66-91) | 19.2 (16.1-24) | 5.1 (3.5-8.1) | 34 (29.3-40.7) | 15.7% (13.1-19.6%) | 8.4% (5.8-13.3%) | 18.1% (15.6-21.7%) |
| France | 101 (0-374) | 11 (0-110) | 90 (0-264) | 1.9 (0-7.2) | 0.4 (0-4.1) | 3.6 (0-10.5) | 1.8% (0-6.7%) | 0.4% (0-4.3%) | 3% (0-8.8%) |
| Gabon | 9 (5-19) | 4 (1-9) | 6 (3-10) | 8.4 (4.3-17.3) | 6.4 (2.6-16.3) | 10.4 (5.9-18.3) | 9.8% (5-20.2%) | 7.2% (2.9-18.1%) | 12.7% (7.2-22.3%) |
| Gambia | 1 (0-1) | 0 (0-1) | 0 (0-1) | 0.6 (0.3-1.3) | 0.4 (0.1-1.1) | 0.8 (0.4-1.5) | 1.1% (0.5-2.3%) | 0.8% (0.3-2.3%) | 1.3% (0.7-2.4%) |
| Georgia | 2 (0-11) | 0 (0-2) | 2 (0-10) | 0.6 (0-3.4) | 0 (0-1) | 1.3 (0-6.2) | 0.7% (0-4.1%) | 0% (0-1.6%) | 1.2% (0-5.6%) |
| Germany | 490 (122-1,261) | 80 (4-316) | 410 (118-945) | 7 (1.7-18) | 2.2 (0.1-8.8) | 12 (3.5-27.6) | 5.6% (1.4-14.3%) | 2.4% (0.1-9.4%) | 7.6% (2.2-17.4%) |
| Ghana | 7 (3-15) | 3 (1-7) | 4 (2-7) | 0.4 (0.2-0.9) | 0.3 (0.1-0.8) | 0.5 (0.2-0.9) | 0.3% (0.2-0.8%) | 0.2% (0.1-0.6%) | 0.5% (0.3-1%) |
| Greece | 7 (0-28) | 0 (0-12) | 7 (0-16) | 0.7 (0-3) | 0 (0-2.4) | 1.5 (0-3.6) | 0.4% (0-1.5%) | 0% (0-1%) | 1% (0-2.4%) |
| Grenada | 0 (0-1) | 0 (0-0) | 0 (0-0) | 0 (0-12.1) | 0 (0-13.8) | 0 (0-10.4) | 0% (0-23.8%) | 0% (0-27.3%) | 0% (0-20.3%) |
| Guatemala | 0 (0-1) | 0 (0-1) | 0 (0-1) | 0 (0-0.1) | 0 (0-0.1) | 0 (0-0.1) | 0% (0-0.6%) | 0% (0-0.7%) | 0% (0-0.6%) |
| Guinea | 1 (0-2) | 0 (0-1) | 1 (0-1) | 0.1 (0.1-0.3) | 0.1 (0-0.3) | 0.2 (0.1-0.4) | 0.3% (0.1-0.7%) | 0.2% (0.1-0.7%) | 0.4% (0.2-0.8%) |
| Guinea-Bissau | 1 (0-2) | 0 (0-1) | 0 (0-1) | 0.7 (0.3-1.4) | 0.4 (0.1-1.1) | 1 (0.5-1.7) | 1.4% (0.7-3%) | 0.9% (0.3-2.6%) | 1.8% (1-3.3%) |
| Guyana | 1 (0-3) | 0 (0-1) | 1 (1-2) | 1.9 (0.5-5) | 0 (0-3.7) | 3.9 (2.5-6.3) | 1.8% (0.4-4.5%) | 0% (0-4%) | 3% (1.9-4.9%) |
| Haiti | 0 (0-6) | 0 (0-3) | 0 (0-3) | 0 (0-1.1) | 0 (0-1.2) | 0 (0-1) | 0% (0-1.1%) | 0% (0-1.1%) | 0% (0-1.1%) |
| Honduras | 0 (0-2) | 0 (0-1) | 0 (0-1) | 0 (0-0.3) | 0 (0-0.3) | 0 (0-0.3) | 0% (0-0.8%) | 0% (0-0.9%) | 0% (0-0.7%) |
| Hungary | 221 (166-359) | 36 (14-126) | 185 (153-233) | 26.2 (19.7-42.5) | 8 (3-28.1) | 46.6 (38.6-58.7) | 14.9% (11.2-24.1%) | 7.7% (2.9-27%) | 18.1% (15-22.8%) |
| Iceland | 1 (1-2) | 0 (0-0) | 1 (1-1) | 4.1 (2.9-6.8) | 0 (0-2) | 8.2 (6.6-11.7) | 11.1% (8-18.5%) | 0% (0-11.9%) | 14.3% (11.5-20.3%) |
| India | 87 | 5 | 81 | 0.1 | 0 | 0.2 | 0.5% | 0.1% | 0.9% |

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|---|---|---|---|---|---|---|---|---|---|
| | (39-199) | (1-25) | (38-174) | (0-0.2) | (0-0.1) | (0.1-0.4) | (0.2-1.2%) | (0-0.3%) | (0.4-1.9%) |
| Indonesia | 13 (4-40) | 3 (1-12) | 10 (4-27) | 0.1 (0-0.2) | 0 (0-0.1) | 0.1 (0-0.3) | 0.1% (0-0.4%) | 0.1% (0-0.2%) | 0.2% (0.1-0.5%) |
| Iran (Islamic Republic of) | 4 (2-12) | 1 (0-3) | 4 (2-8) | 0.1 (0-0.2) | 0 (0-0.1) | 0.1 (0.1-0.3) | 0.2% (0.1-0.5%) | 0.1% (0-0.3%) | 0.3% (0.1-0.6%) |
| Iraq | 3 (1-8) | 1 (0-4) | 2 (1-4) | 0.1 (0.1-0.4) | 0.1 (0-0.4) | 0.2 (0.1-0.4) | 0.2% (0.1-0.5%) | 0.1% (0-0.4%) | 0.2% (0.1-0.5%) |
| Ireland | 11 (2-28) | 2 (0-9) | 9 (3-18) | 3 (0.4-7.6) | 1.1 (0-5.1) | 5 (1.6-10.2) | 5.3% (0.7-13.4%) | 2.9% (0-13.4%) | 6.5% (2.1-13.3%) |
| Israel | 1 (0-2) | 0 (0-1) | 1 (1-2) | 0.2 (0.1-0.4) | 0 (0-0.2) | 0.4 (0.2-0.6) | 0.5% (0.2-1.2%) | 0% (0-0.6%) | 0.9% (0.5-1.6%) |
| Italy | 17 (0-73) | 3 (0-21) | 14 (0-52) | 0.3 (0-1.4) | 0.1 (0-0.8) | 0.6 (0-2.1) | 0.3% (0-1.4%) | 0.1% (0-0.9%) | 0.5% (0-1.9%) |
| Jamaica | 2 (1-3) | 0 (0-1) | 2 (2-3) | 1 (0.6-1.7) | 0 (0-0.6) | 2 (1.6-2.8) | 1.4% (0.9-2.4%) | 0% (0-1%) | 2.5% (2-3.4%) |
| Japan | 45 (2-128) | 2 (0-27) | 43 (9-101) | 0.4 (0-1.2) | 0 (0-0.5) | 0.8 (0.2-1.9) | 0.6% (0-1.6%) | 0% (0-0.7%) | 1.1% (0.2-2.6%) |
| Jordan | 0 (0-1) | 0 (0-0) | 0 (0-0) | 0 (0-0.1) | 0 (0-0.2) | 0 (0-0.1) | 0% (0-0.5%) | 0% (0-0.6%) | 0% (0-0.5%) |
| Kazakhstan | 34 (23-49) | 4 (2-7) | 30 (21-43) | 2.6 (1.8-3.8) | 0.5 (0.3-1) | 5 (3.5-7) | 2.4% (1.7-3.5%) | 0.7% (0.4-1.3%) | 3.3% (2.4-4.7%) |
| Kenya | 5 (2-9) | 1 (0-2) | 4 (2-7) | 0.2 (0.1-0.3) | 0.1 (0-0.2) | 0.3 (0.2-0.5) | 0.5% (0.2-0.9%) | 0.2% (0.1-0.6%) | 0.7% (0.4-1.2%) |
| Kiribati | 0 (0-0) | 0 (0-0) | 0 (0-0) | 0 (0-7) | 0 (0-11) | 0 (0-2.7) | 0% (0-5.9%) | 0% (0-9.7%) | 0% (0-2.2%) |
| Kuwait | 0 (0-0) | 0 (0-0) | 0 (0-0) | 0 (0-0.1) | 0 (0-0.2) | 0 (0-0.1) | 0% (0-0.6%) | 0% (0-0.7%) | 0% (0-0.4%) |
| Kyrgyzstan | 271 (267-277) | 51 (50-52) | 220 (216-225) | 67.3 (66.2-68.7) | 24.7 (24.5-25.1) | 112 (110.2-114.5) | 67.9% (66.9-69.4%) | 54.3% (53.7-55.2%) | 72.1% (70.9-73.7%) |
| Lao People's Democratic Republic | 14 (9-22) | 3 (2-6) | 11 (7-16) | 3.1 (1.9-4.9) | 1.3 (0.7-2.4) | 4.9 (3.3-7.5) | 4.8% (3-7.7%) | 1.8% (0.9-3.4%) | 9% (5.9-13.6%) |
| Latvia | 271 (222-353) | 55 (49-67) | 216 (174-287) | 159.5 (130.8-208) | 58.7 (52-71.3) | 283.2 (227.5-375.7) | 33.9% (27.8-44.2%) | 21% (18.6-25.5%) | 40.1% (32.3-53.3%) |
| Lebanon | 1 (0-3) | 0 (0-1) | 1 (0-2) | 0.3 (0.1-0.6) | 0.2 (0.1-0.6) | 0.3 (0.2-0.7) | 0.4% (0.2-0.9%) | 0.3% (0.1-0.9%) | 0.4% (0.2-0.9%) |
| Lesotho | 2 (1-4) | 1 (0-2) | 1 (1-2) | 1.5 (0.8-2.9) | 1.3 (0.5-3) | 1.7 (1.1-2.8) | 1.2% (0.7-2.4%) | 0.9% (0.4-2.2%) | 1.7% (1.1-2.9%) |
| Liberia | 2 (1-3) | 0 (0-1) | 1 (1-2) | 0.7 (0.4-1.2) | 0.3 (0.1-0.6) | 1 (0.7-1.7) | 1.7% (1-2.9%) | 0.9% (0.4-1.9%) | 2.3% (1.4-3.6%) |
| Libya | 1 (0-2) | 0 (0-1) | 0 (0-1) | 0.2 (0.1-0.5) | 0.2 (0.1-0.6) | 0.2 (0.1-0.5) | 0.2% (0.1-0.7%) | 0.2% (0.1-0.8%) | 0.3% (0.1-0.6%) |
| Lithuania | 95 (0-230) | 21 (11-48) | 74 (0-359) | 38 (0-91.9) | 15.3 (8-34.7) | 65.6 (0-161.5) | 20.2% (0-48.7%) | 18.8% (9.8-42.4%) | 20.6% (0-50.7%) |
| Luxembourg | 0 (0-13) | 0 (0-10) | 0 (0-2) | 0 (0-27.7) | 0 (0-44.5) | 0 (0-10.7) | 0% (0-37.7%) | 0% (0-54.5%) | 0% (0-16.5%) |
| Madagascar | 3 (1-7) | 1 (0-2) | 2 (1-4) | 0.2 (0.1-0.5) | 0.1 (0-0.4) | 0.3 (0.2-0.6) | 0.3% (0.1-0.7%) | 0.2% (0.1-0.6%) | 0.4% (0.2-0.8%) |
| Malawi | 3 (1-5) | 1 (0-2) | 2 (1-3) | 0.3 (0.1-0.5) | 0.1 (0.1-0.3) | 0.4 (0.2-0.7) | 0.6% (0.3-1.2%) | 0.3% (0.1-0.8%) | 0.9% (0.5-1.5%) |
| Malaysia | 3 (1-7) | 1 (0-2) | 2 (1-5) | 0.1 (0.1-0.3) | 0.1 (0-0.2) | 0.2 (0.1-0.4) | 0.2% (0.1-0.5%) | 0.2% (0.1-0.5%) | 0.3% (0.1-0.6%) |
| Maldives | 0 (0-0) | 0 (0-0) | 0 (0-0) | 0 (0-0.7) | 0 (0-1) | 0 (0-0.4) | 0% (0-2.4%) | 0% (0-2.9%) | 0% (0-1.6%) |
| Mali | 2 (1-4) | 1 (0-2) | 1 (0-2) | 0.2 (0.1-0.4) | 0.1 (0-0.4) | 0.2 (0.1-0.4) | 0.3% (0.1-0.7%) | 0.2% (0.1-0.6%) | 0.4% (0.2-0.8%) |
| Malta | 1 (0-2) | 0 (0-0) | 1 (1-2) | 2.8 (1.5-5.8) | 0 (0-2.9) | 5.7 (4.2-8.8) | 5.9% (3.2-12.1%) | 0% (0-7.4%) | 10% (7.3-15.4%) |
| Marshall Islands | 0 (0-0) | 0 (0-0) | 0 (0-0) | 2.7 (0.7-11) | 3.8 (0.8-17.8) | 1.5 (0.6-4.2) | 2.3% (0.6-9.4%) | 3.2% (0.7-15.3%) | 1.3% (0.5-3.6%) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Mauritania | 0 (0-1) | 0 (0-0) | 0 (0-0) | 0.1 (0.1-0.4) | 0.1 (0-0.4) | 0.2 (0.1-0.3) | 0.3% (0.1-0.8%) | 0.3% (0.1-1%) | 0.3% (0.1-0.7%) |
| Mauritius | 0 (0-1) | 0 (0-0) | 0 (0-0) | 0 (0-0.7) | 0 (0-0.6) | 0 (0-0.8) | 0% (0-1.1%) | 0% (0-1.4%) | 0% (0-0.9%) |
| Mexico | 37 (30-50) | 2 (1-5) | 35 (29-44) | 0.4 (0.3-0.6) | 0 (0-0.1) | 0.8 (0.6-1) | 2% (1.6-2.7%) | 0.3% (0.1-0.7%) | 3.4% (2.8-4.3%) |
| Micronesia (Federated States of) | 0 (0-1) | 0 (0-0) | 0 (0-0) | 2.4 (0.7-8.8) | 3.6 (0.9-14.7) | 1.3 (0.5-3.2) | 1.8% (0.5-6.8%) | 2.4% (0.6-10%) | 1.1% (0.5-2.8%) |
| Monaco | 2 (0-4) | 2 (0-2) | 1 (0-2) | 69.7 (15.8-125.3) | 91.5 (16.2-124.2) | 47.5 (15.4-126.4) | 55.6% (12.6-100%) | 73.7% (13-100%) | 37.6% (12.2-100%) |
| Mongolia | 5 (3-7) | 1 (0-2) | 4 (3-6) | 2.2 (1.5-3.4) | 0.7 (0.4-1.3) | 3.8 (2.6-5.6) | 2.9% (1.9-4.5%) | 1.4% (0.7-2.6%) | 3.8% (2.6-5.6%) |
| Montenegro | 9 (5-18) | 5 (2-11) | 5 (3-7) | 18.3 (10.2-34.5) | 17.9 (7.8-41.2) | 18.7 (12.7-27.5) | 4.1% (2.3-7.8%) | 3.8% (1.6-8.7%) | 4.6% (3.1-6.8%) |
| Morocco | 0 (0-6) | 0 (0-3) | 0 (0-3) | 0 (0-0.3) | 0 (0-0.3) | 0 (0-0.2) | 0% (0-0.3%) | 0% (0-0.3%) | 0% (0-0.3%) |
| Mozambique | 3 (2-7) | 1 (0-3) | 2 (1-4) | 0.2 (0.1-0.4) | 0.1 (0-0.4) | 0.3 (0.2-0.5) | 0.3% (0.2-0.8%) | 0.2% (0.1-0.6%) | 0.5% (0.3-1%) |
| Myanmar | 19 (10-37) | 5 (2-14) | 14 (8-23) | 0.5 (0.2-1) | 0.3 (0.1-0.7) | 0.7 (0.4-1.2) | 0.5% (0.3-1%) | 0.2% (0.1-0.6%) | 1% (0.6-1.7%) |
| Namibia | 9 (5-15) | 2 (1-3) | 7 (4-12) | 5.7 (3.4-9.6) | 2 (1-3.9) | 9.7 (6-15.8) | 6.2% (3.7-10.4%) | 2.3% (1.2-4.4%) | 10.2% (6.3-16.5%) |
| Nauru | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Nepal | 1 (0-2) | 0 (0-1) | 1 (0-1) | 0 (0-0.1) | 0 (0-0.1) | 0.1 (0-0.2) | 0.4% (0.2-0.8%) | 0.2% (0.1-0.5%) | 0.6% (0.3-1%) |
| Netherlands | 17 (4-41) | 2 (0-16) | 15 (8-25) | 1.2 (0.3-2.9) | 0.3 (0-2.2) | 2.2 (1.1-3.6) | 1.3% (0.3-3.2%) | 0.3% (0-2.4%) | 2.4% (1.2-4%) |
| New Zealand | 15 (8-28) | 3 (0-9) | 12 (7-19) | 4.3 (2.1-8) | 1.6 (0.2-4.9) | 7 (4.2-11.3) | 6% (3-11.3%) | 3.2% (0.4-9.5%) | 7.7% (4.6-12.4%) |
| Nicaragua | 0 (0-2) | 0 (0-1) | 0 (0-1) | 0 (0-0.3) | 0 (0-0.3) | 0 (0-0.4) | 0% (0-1%) | 0% (0-1.1%) | 0% (0-1%) |
| Niger | 1 (0-2) | 0 (0-1) | 1 (0-1) | 0.1 (0-0.2) | 0.1 (0-0.2) | 0.1 (0.1-0.2) | 0.2% (0.1-0.6%) | 0.2% (0.1-0.6%) | 0.3% (0.1-0.6%) |
| Nigeria | 502 (277-931) | 24 (7-86) | 478 (270-846) | 4.9 (2.7-9.1) | 0.5 (0.1-1.7) | 9.2 (5.2-16.3) | 7.9% (4.4-14.7%) | 0.9% (0.3-3.4%) | 12.6% (7.1-22.3%) |
| Niue | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Norway | 9 (5-20) | 1 (0-10) | 8 (7-10) | 2.1 (1.2-4.7) | 0.5 (0-4.7) | 3.8 (3.2-4.6) | 4.2% (2.4-9.2%) | 1.1% (0-10.8%) | 6.6% (5.6-8%) |
| Oman | 0 (0-0) | 0 (0-0) | 0 (0-0) | 0 (0-0.2) | 0 (0-0.2) | 0 (0-0.1) | 0% (0-0.6%) | 0% (0-0.8%) | 0% (0-0.4%) |
| Pakistan | 3 (1-9) | 1 (0-3) | 2 (1-6) | 0 (0-0.1) | 0 (0-0) | 0 (0-0.1) | 0.1% (0.1-0.4%) | 0.1% (0-0.3%) | 0.2% (0.1-0.5%) |
| Palau | 0 (0-0) | 0 (0-0) | 0 (0-0) | 3.3 (0.6-18.2) | 5.4 (0.9-32.6) | 1.1 (0.3-3.5) | 2.2% (0.4-12.3%) | 3.7% (0.6-22.3%) | 0.7% (0.2-2.3%) |
| Panama | 0 (0-4) | 0 (0-1) | 0 (0-3) | 0 (0-1.4) | 0 (0-0.9) | 0 (0-1.9) | 0% (0-1.8%) | 0% (0-1.7%) | 0% (0-1.8%) |
| Papua New Guinea | 2 (1-4) | 1 (0-2) | 1 (0-2) | 0.4 (0.2-0.9) | 0.4 (0.2-1) | 0.4 (0.2-0.8) | 0.4% (0.2-0.8%) | 0.3% (0.1-0.9%) | 0.4% (0.2-0.8%) |
| Paraguay | 1 (0-4) | 0 (0-1) | 1 (0-3) | 0.2 (0-0.9) | 0 (0-0.5) | 0.4 (0-1.3) | 0.5% (0-1.9%) | 0% (0-1.2%) | 0.9% (0-2.6%) |
| Peru | 0 (0-8) | 0 (0-4) | 0 (0-4) | 0 (0-0.4) | 0 (0-0.3) | 0 (0-0.4) | 0% (0-0.8%) | 0% (0-0.8%) | 0% (0-0.9%) |
| Philippines | 15 (0-41) | 1 (0-7) | 14 (1-34) | 0.2 (0-0.7) | 0 (0-0.2) | 0.5 (0-1.1) | 0.5% (0-1.3%) | 0.1% (0-0.5%) | 0.8% (0.1-1.9%) |
| Poland | 415 (153-899) | 42 (0-185) | 373 (182-714) | 12.6 (4.7-27.4) | 2.5 (0-10.8) | 23.7 (11.6-45.4) | 3.3% (1.2-7.1%) | 0.6% (0-2.8%) | 6.4% (3.1-12.2%) |
| Portugal | 15 (0-53) | 0 (0-13) | 15 (0-40) | 1.7 (0-5.9) | 0 (0-2.8) | 3.6 (0-9.6) | 2.3% (0-8.2%) | 0% (0-4.9%) | 3.9% (0-10.5%) |
| Qatar | 0 (0-0) | 0 (0-0) | 0 (0-0) | 0.1 (0-0.1) | 0 (0-0.1) | 0.1 (0-0.1) | 0.6% (0.3-1.5%) | 0.6% (0.2-1.9%) | 0.6% (0.3-1.4%) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Republic of Korea | 1 (0-35) | 0 (0-17) | 1 (0-18) | 0 (0-1) | 0 (0-0.9) | 0.1 (0-1) | 0.1% (0-2.3%) | 0% (0-2.1%) | 0.1% (0-2.6%) |
| Republic of Moldova | 125 (8-240) | 31 (24-48) | 94 (0-299) | 36.5 (2.5-69.9) | 17.2 (13.5-26.8) | 57.8 (0-117.7) | 28.4% (1.9-54.5%) | 22% (17.3-34.2%) | 31.4% (0-64%) |
| Romania | 70 (0-350) | 12 (0-87) | 58 (0-262) | 4.2 (0-21.1) | 1.4 (0-10.1) | 7.3 (0-33) | 1.8% (0-9.2%) | 0.8% (0-5.6%) | 2.6% (0-11.7%) |
| Russian Federation | 19,749 (14,320-35,136) | 4,871 (4,236-7,896) | 14,878 (10,084-27,240) | 163.8 (118.8-291.4) | 74.1 (64.5-120.2) | 271.2 (183.8-496.5) | 26.7% (19.4-47.5%) | 18.4% (16-29.9%) | 31.3% (21.2-57.4%) |
| Rwanda | 16 (11-23) | 2 (1-3) | 14 (10-20) | 2.3 (1.6-3.4) | 0.4 (0.2-0.7) | 4.6 (3.3-6.4) | 4.6% (3.2-6.6%) | 1.3% (0.7-2.1%) | 6.4% (4.5-8.9%) |
| Saint Kitts and Nevis | 0 (0-1) | 0 (0-1) | 0 (0-0) | 0 (0-18.1) | 0 (0-29.8) | 0 (0-6.3) | 0% (0-24.9%) | 0% (0-30.9%) | 0% (0-12.9%) |
| Saint Lucia | 4 (3-7) | 1 (0-2) | 3 (2-4) | 28.9 (20.8-48.2) | 14.1 (6.9-35.3) | 44.5 (35.4-61.8) | 16% (11.5-26.7%) | 11.1% (5.5-27.9%) | 18.8% (14.9-26.1%) |
| Saint Vincent and the Grenadines | 0 (0-0) | 0 (0-0) | 0 (0-0) | 0 (0-6.5) | 0 (0-4.7) | 0 (0-8.3) | 0% (0-10.7%) | 0% (0-19.1%) | 0% (0-8.6%) |
| Samoa | 0 (0-1) | 0 (0-0) | 0 (0-0) | 1.8 (0.6-5.7) | 2.3 (0.6-8.4) | 1.4 (0.6-3.2) | 1.4% (0.5-4.3%) | 1.9% (0.5-7.1%) | 1% (0.4-2.2%) |
| San Marino | 0 (0-2) | 0 (0-2) | 0 (0-0) | 19.4 (4.7-87.5) | 28.2 (5.4-146.1) | 10.5 (4-27.9) | 10.5% (2.5-47%) | 12.7% (2.5-66%) | 7% (2.7-18.6%) |
| Sao Tome and Principe | 0 (0-1) | 0 (0-0) | 0 (0-0) | 2.7 (1-7.8) | 2.4 (0.7-8.1) | 3 (1.2-7.4) | 5% (1.8-14.2%) | 4.5% (1.3-15%) | 5.4% (2.2-13.4%) |
| Saudi Arabia | 0 (0-4) | 0 (0-2) | 0 (0-2) | 0 (0-0.2) | 0 (0-0.3) | 0 (0-0.2) | 0% (0-0.3%) | 0% (0-0.3%) | 0% (0-0.3%) |
| Senegal | 1 (0-2) | 0 (0-1) | 1 (0-1) | 0.1 (0-0.3) | 0.1 (0-0.2) | 0.1 (0.1-0.3) | 0.3% (0.1-0.7%) | 0.2% (0.1-0.6%) | 0.3% (0.2-0.7%) |
| Serbia | 20 (0-488) | 1 (0-163) | 19 (0-325) | 2.7 (0-65.9) | 0.3 (0-42.6) | 5.3 (0-90.7) | 0.1% (0-3.3%) | 0% (0-1.9%) | 0.3% (0-5.1%) |
| Seychelles | 1 (0-4) | 0 (0-1) | 1 (0-3) | 17.5 (5.7-53.5) | 6.2 (1.5-26.1) | 28.6 (9.9-80.4) | 32.4% (10.6-98.8%) | 22.6% (5.4-95.4%) | 35.6% (12.3-100%) |
| Sierra Leone | 4 (2-6) | 1 (0-2) | 3 (2-4) | 0.9 (0.6-1.6) | 0.5 (0.2-1.1) | 1.4 (1-2.2) | 1.3% (0.8-2.3%) | 0.7% (0.3-1.6%) | 1.9% (1.3-2.9%) |
| Singapore | 2 (1-3) | 0 (0-1) | 2 (2-3) | 0.4 (0.3-0.7) | 0 (0-0.3) | 0.9 (0.7-1.2) | 0.8% (0.6-1.3%) | 0% (0-0.6%) | 1.4% (1.2-1.9%) |
| Slovakia | 99 (85-121) | 11 (9-16) | 88 (76-106) | 21.5 (18.5-26.3) | 4.6 (3.7-6.5) | 39.8 (34.6-47.8) | 27.6% (23.8-33.7%) | 12% (9.6-16.8%) | 33% (28.6-39.5%) |
| Slovenia | 60 (31-121) | 12 (0-51) | 48 (35-71) | 34 (17.4-68.7) | 13.4 (0-56.6) | 55.2 (39.9-81.2) | 16.3% (8.3-33%) | 5.9% (0-25%) | 29.1% (21-42.8%) |
| Solomon Islands | 0 (0-1) | 0 (0-1) | 0 (0-0) | 0.8 (0.3-2.4) | 1.1 (0.3-3.4) | 0.6 (0.3-1.3) | 0.8% (0.3-2.4%) | 1.1% (0.3-3.4%) | 0.6% (0.3-1.4%) |
| Somalia | 1 (0-2) | 0 (0-1) | 0 (0-1) | 0.1 (0.1-0.3) | 0.1 (0-0.4) | 0.1 (0.1-0.3) | 0.2% (0.1-0.6%) | 0.2% (0.1-0.7%) | 0.3% (0.1-0.6%) |
| South Africa | 149 (91-246) | 13 (6-28) | 135 (84-217) | 3.9 (2.4-6.4) | 0.7 (0.3-1.4) | 7.2 (4.5-11.6) | 2.6% (1.6-4.3%) | 0.5% (0.2-1.1%) | 4.4% (2.7-7%) |
| Spain | 26 (0-138) | 2 (0-41) | 24 (0-97) | 0.7 (0-3.5) | 0.1 (0-2) | 1.3 (0-5.1) | 0.6% (0-2.9%) | 0.1% (0-2%) | 0.9% (0-3.6%) |
| Sri Lanka | 6 (4-9) | 0 (0-1) | 6 (5-8) | 0.4 (0.3-0.6) | 0 (0-0.1) | 0.8 (0.7-1.2) | 0.8% (0.6-1.3%) | 0% (0-0.4%) | 1.3% (1-1.8%) |
| Sudan | 4 (2-12) | 2 (0-6) | 3 (1-6) | 0.2 (0.1-0.5) | 0.1 (0-0.5) | 0.2 (0.1-0.5) | 0.2% (0.1-0.5%) | 0.1% (0-0.4%) | 0.2% (0.1-0.5%) |
| Suriname | 0 (0-2) | 0 (0-1) | 0 (0-1) | 0 (0-4.7) | 0 (0-6.2) | 0 (0-3.2) | 0% (0-4.3%) | 0% (0-5.4%) | 0% (0-3.1%) |
| Swaziland | 7 (4-13) | 2 (1-4) | 5 (3-9) | 8.7 (4.9-15.8) | 4.5 (2.1-9.6) | 13.1 (7.7-22.3) | 6.5% (3.6-11.7%) | 3.1% (1.5-6.6%) | 10.6% (6.2-18%) |
| Sweden | 26 (17-48) | 3 (0-20) | 23 (19-28) | 3.2 (2.1-6) | 0.7 (0-5) | 5.8 (4.8-7) | 4.7% (3.1-8.6%) | 1.5% (0-10.1%) | 6.4% (5.4-7.8%) |
| Switzerland | 16 | 2 | 14 | 2.3 | 0.6 | 4.1 | 1.8% | 0.4% | 3.2% |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | (0-59) | (0-29) | (3-30) | (0-8.5) | (0-8.3) | (0.9-8.8) | (0-6.6%) | (0-6.4%) | (0.7-6.8%) |
| Syrian Arab Republic | 3 (1-7) | 1 (0-3) | 2 (1-4) | 0.2 (0.1-0.6) | 0.2 (0.1-0.6) | 0.3 (0.1-0.7) | 0.2% (0.1-0.5%) | 0.2% (0.1-0.5%) | 0.2% (0.1-0.5%) |
| Tajikistan | 2 (1-3) | 0 (0-1) | 1 (1-2) | 0.3 (0.2-0.6) | 0.1 (0-0.3) | 0.5 (0.3-0.8) | 0.7% (0.4-1.3%) | 0.4% (0.1-1%) | 0.8% (0.5-1.5%) |
| Thailand | 0 (0-25) | 0 (0-8) | 0 (0-17) | 0 (0-0.5) | 0 (0-0.3) | 0 (0-0.7) | 0% (0-0.8%) | 0% (0-0.5%) | 0% (0-1.1%) |
| The former Yugoslav Republic of Macedonia | 73 (44-122) | 36 (19-67) | 37 (25-55) | 42.2 (25.4-70.7) | 41.1 (22.1-76.5) | 43.3 (28.9-64.9) | 2.3% (1.4-3.8%) | 2.1% (1.1-3.8%) | 2.6% (1.7-3.9%) |
| Timor-Leste | 0 (0-1) | 0 (0-0) | 0 (0-0) | 0.4 (0.2-1.2) | 0.5 (0.2-1.5) | 0.4 (0.2-0.9) | 0.8% (0.3-2%) | 0.8% (0.2-2.3%) | 0.8% (0.4-1.6%) |
| Togo | 2 (1-3) | 1 (0-2) | 1 (0-2) | 0.4 (0.2-0.8) | 0.3 (0.1-0.8) | 0.4 (0.3-0.8) | 0.7% (0.4-1.6%) | 0.7% (0.3-1.7%) | 0.8% (0.5-1.5%) |
| Tonga | 0 (0-0) | 0 (0-0) | 0 (0-0) | 1.4 (0.4-5.1) | 1.9 (0.5-8) | 0.8 (0.3-2.1) | 1.5% (0.4-5.7%) | 2.2% (0.5-9.1%) | 0.9% (0.3-2.3%) |
| Trinidad and Tobago | 2 (1-4) | 0 (0-1) | 2 (1-3) | 1.9 (1-3.5) | 0 (0-1.3) | 3.9 (2.7-5.8) | 2.6% (1.3-4.7%) | 0% (0-2.9%) | 3.7% (2.6-5.5%) |
| Tunisia | 0 (0-3) | 0 (0-2) | 0 (0-2) | 0 (0-0.4) | 0 (0-0.4) | 0 (0-0.4) | 0% (0-0.4%) | 0% (0-0.4%) | 0% (0-0.4%) |
| Turkey | 2 (0-14) | 0 (0-4) | 2 (0-10) | 0 (0-0.2) | 0 (0-0.1) | 0.1 (0-0.4) | 0.1% (0-0.4%) | 0% (0-0.3%) | 0.1% (0-0.6%) |
| Turkmenistan | 3 (2-6) | 1 (0-1) | 3 (2-4) | 0.9 (0.6-1.4) | 0.4 (0.2-0.7) | 1.5 (1-2.2) | 1.4% (0.9-2.3%) | 0.8% (0.4-1.5%) | 1.8% (1.2-2.7%) |
| Tuvalu | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Uganda | 36 (25-52) | 4 (2-8) | 32 (23-44) | 1.8 (1.2-2.6) | 0.4 (0.2-0.8) | 3.2 (2.3-4.4) | 3.2% (2.3-4.7%) | 0.8% (0.4-1.5%) | 5.5% (4-7.6%) |
| Ukraine | 291 (162-524) | 13 (6-28) | 278 (156-496) | 7.6 (4.2-13.7) | 0.6 (0.3-1.3) | 16.1 (9-28.7) | 3.1% (1.7-5.6%) | 0.5% (0.2-1%) | 4.2% (2.4-7.6%) |
| United Arab Emirates | 2 (1-3) | 0 (0-0) | 1 (1-2) | 0.2 (0.1-0.4) | 0.1 (0-0.2) | 0.2 (0.1-0.4) | 0.6% (0.3-1.1%) | 0.4% (0.1-1%) | 0.6% (0.3-1.1%) |
| United Kingdom | 102 (24-324) | 17 (0-177) | 85 (44-147) | 1.9 (0.5-6.1) | 0.6 (0-6.6) | 3.3 (1.7-5.7) | 3.5% (0.8-11%) | 1.4% (0-14.1%) | 5% (2.6-8.7%) |
| United Republic of Tanzania | 51 (35-74) | 5 (2-10) | 46 (32-65) | 1.7 (1.2-2.5) | 0.3 (0.2-0.6) | 3.2 (2.3-4.5) | 3.2% (2.2-4.6%) | 0.7% (0.4-1.4%) | 5.1% (3.6-7.2%) |
| United States of America | 526 (176-1,364) | 81 (1-352) | 445 (175-1,013) | 2 (0.7-5.3) | 0.6 (0-2.7) | 3.5 (1.4-8) | 1.7% (0.6-4.3%) | 0.6% (0-2.6%) | 2.4% (1-5.6%) |
| Uruguay | 2 (0-16) | 0 (0-6) | 2 (0-10) | 0.7 (0-6) | 0 (0-4.5) | 1.6 (0-7.7) | 0.6% (0-4.9%) | 0% (0-4.4%) | 1.1% (0-5.2%) |
| Uzbekistan | 2 (1-5) | 0 (0-1) | 2 (1-4) | 0.1 (0.1-0.2) | 0 (0-0.1) | 0.2 (0.1-0.4) | 0.5% (0.3-0.9%) | 0.2% (0.1-0.6%) | 0.6% (0.3-1.1%) |
| Vanuatu | 0 (0-0) | 0 (0-0) | 0 (0-0) | 0.8 (0.3-2.7) | 1.1 (0.3-4.1) | 0.5 (0.2-1.3) | 1% (0.3-3.3%) | 1.4% (0.4-5%) | 0.6% (0.3-1.6%) |
| Venezuela (Bolivarian Republic of) | 6 (1-13) | 1 (0-3) | 5 (2-10) | 0.3 (0.1-0.6) | 0.1 (0-0.3) | 0.5 (0.1-0.9) | 0.9% (0.2-2%) | 0.4% (0-1.2%) | 1.3% (0.4-2.6%) |
| Viet Nam | 18 (9-36) | 2 (1-6) | 16 (9-30) | 0.3 (0.1-0.5) | 0.1 (0-0.2) | 0.5 (0.2-0.8) | 0.5% (0.3-1.1%) | 0.2% (0.1-0.5%) | 0.8% (0.4-1.5%) |
| Yemen | 3 (1-7) | 1 (0-4) | 2 (1-4) | 0.2 (0.1-0.5) | 0.1 (0-0.5) | 0.2 (0.1-0.5) | 0.2% (0.1-0.5%) | 0.1% (0-0.5%) | 0.2% (0.1-0.5%) |
| Zambia | 4 (2-6) | 1 (0-2) | 3 (2-4) | 0.4 (0.2-0.7) | 0.2 (0.1-0.4) | 0.6 (0.4-1) | 0.9% (0.6-1.6%) | 0.4% (0.2-1%) | 1.4% (0.9-2.1%) |
| Zimbabwe | 8 (4-13) | 2 (1-4) | 6 (4-9) | 0.8 (0.5-1.4) | 0.4 (0.2-0.8) | 1.3 (0.8-2) | 0.9% (0.5-1.5%) | 0.4% (0.2-1%) | 1.2% (0.8-1.9%) |

Note: ACM = alcoholic cardiomyopathic deaths according to ICD-10 (code I42.6). Mortality rate = number of deaths per 1,000,000 adult population. NA = number of CM deaths = 0, which implies no plausible predictions for these countries. Number in bracket denote 95% confidence interval.

**Table B.4** Recorded and predicted number of alcoholic cardiomyopathy deaths, alcoholic cardiomyopathy mortality rates, and alcohol-attributable fractions

| Country | ACM death counts | | Mortality rate | | Alcohol-attributable fraction | |
|---|---|---|---|---|---|---|
| | Observed | Predicted | Observed | Predicted | Observed | Predicted |
| Antigua and Barbuda | 0 | 0 (0-1) | 0.0 | 3.2 (1-10.8) | 0% | 7.4% (2.2-24.7%) |
| Argentina | 8 | 133 (81-219) | 0.3 | 4.2 (2.5-6.9) | 0.1% | 2.5% (1.5-4.1%) |
| Australia | 58 | 68 (45-106) | 3.0 | 3.5 (2.3-5.5) | 4.1% | 4.9% (3.2-7.6%) |
| Austria | 12 | 158 (81-338) | 1.6 | 21.6 (11-46.2) | 0.9% | 11.3% (5.8-24.2%) |
| Bahamas | 0 | 1 (0-2) | 0.0 | 3.1 (1.4-7.1) | 0% | 2.3% (1-5.3%) |
| Barbados | 0 | 2 (1-5) | 0.0 | 10.6 (5.2-22.1) | 0% | 6.5% (3.2-13.5%) |
| Belgium | 23 | 78 (47-130) | 2.5 | 8.4 (5.1-14) | 2.2% | 7.5% (4.6-12.6%) |
| Belize | 0 | 1 (0-2) | 0.0 | 3 (1.4-6.4) | 0% | 3.9% (1.9-8.4%) |
| Bolivia (Plurinational State of) | 0 | 5 (2-10) | 0.0 | 0.9 (0.5-1.8) | 0% | 0.7% (0.4-1.5%) |
| Brazil | 259 | 291 (144-593) | 1.6 | 1.8 (0.9-3.8) | 1.4% | 1.6% (0.8-3.3%) |
| Bulgaria | 8 | 172 (107-277) | 1.3 | 27.6 (17.2-44.6) | 0.3% | 6.6% (4.1-10.6%) |
| Canada | 59 | 50 (34-77) | 2.0 | 1.7 (1.2-2.6) | 4% | 3.4% (2.3-5.2%) |
| Chile | 13 | 26 (18-38) | 0.9 | 1.8 (1.3-2.7) | 1.6% | 3.3% (2.3-4.7%) |
| Colombia | 0 | 13 (8-23) | 0.0 | 0.4 (0.2-0.7) | 0% | 0.9% (0.5-1.6%) |
| Costa Rica | 5 | 3 (2-5) | 1.4 | 0.8 (0.4-1.4) | 1.9% | 1.1% (0.6-1.9%) |
| Croatia | 39 | 21 (14-32) | 10.8 | 5.9 (3.9-8.8) | 11.3% | 6.2% (4.1-9.2%) |
| Cuba | 84 | 10 (7-17) | 8.8 | 1.1 (0.7-1.8) | 10.3% | 1.3% (0.8-2.1%) |
| Cyprus | 1 | 5 (3-9) | 1.0 | 5 (2.7-9.5) | 1.8% | 8.4% (4.5-16%) |
| Czechia | 24 | 117 (65-220) | 2.7 | 13.1 (7.2-24.6) | 3.8% | 18.8% (10.3-35.2%) |
| Denmark | 6 | 16 (10-24) | 1.3 | 3.4 (2.2-5.2) | 2.3% | 6.1% (4-9.4%) |
| Dominica | 0 | 1 (0-3) | 0.0 | 20.2 (7.4-60) | 0% | 7.2% (2.7-21.5%) |
| Dominican Republic | 1 | 6 (4-10) | 0.1 | 0.8 (0.5-1.4) | 0.3% | 1.8% (1.1-2.8%) |
| Ecuador | 2 | 4 (2-6) | 0.2 | 0.3 (0.2-0.6) | 0.6% | 1.1% (0.7-1.9%) |
| El Salvador | 0 | 1 (1-2) | 0.0 | 0.3 (0.2-0.6) | 0% | 0.9% (0.5-1.7%) |
| Estonia | 73 | 62 (33-116) | 65.3 | 55.1 (29.1-104.2) | 30.7% | 25.9% (13.7-48.9%) |
| Fiji | 0 | 1 (0-2) | 0.0 | 1.5 (0.7-3.4) | 0% | 1% (0.4-2.2%) |
| Finland | 88 | 43 (29-65) | 19.2 | 9.4 (6.3-14.2) | 15.7% | 7.7% (5.1-11.6%) |
| France | 101 | 333 (188-606) | 1.9 | 6.4 (3.6-11.6) | 1.8% | 6% (3.4-10.9%) |
| Georgia | 2 | 17 (11-27) | 0.6 | 5.2 (3.4-8) | 0.7% | 6.2% (4.1-9.6%) |
| Germany | 490 | 753 (386-1,524) | 7.0 | 10.7 (5.5-21.7) | 5.6% | 8.6% (4.4-17.3%) |
| Greece | 7 | 44 (30-65) | 0.7 | 4.6 (3.2-6.9) | 0.4% | 2.4% (1.6-3.5%) |
| Grenada | 0 | 0 (0-1) | 0.0 | 5.9 (1.9-18) | 0% | 11.5% (3.8-35.3%) |
| Guatemala | 0 | 1 (1-2) | 0.0 | 0.1 (0.1-0.2) | 0% | 0.6% (0.3-1.2%) |
| Guyana | 1 | 2 (1-3) | 1.9 | 2.9 (1.5-6) | 1.8% | 2.7% (1.3-5.4%) |
| Haiti | 0 | 11 (7-17) | 0.0 | 2 (1.3-3.1) | 0% | 1.9% (1.2-3%) |
| Honduras | 0 | 2 (1-3) | 0.0 | 0.3 (0.2-0.6) | 0% | 0.9% (0.5-1.8%) |
| Hungary | 221 | 126 (72-264) | 26.2 | 14.9 (8.5-31.3) | 14.9% | 8.5% (4.8-17.8%) |
| Iceland | 1 | 0 (0-1) | 4.1 | 2.1 (0.9-4.8) | 11.1% | 5.6% (2.4-12.9%) |
| Ireland | 11 | 23 (14-40) | 3.0 | 6.3 (3.7-10.9) | 5.3% | 11% (6.5-19.1%) |
| Israel | 1 | 2 (1-3) | 0.2 | 0.3 (0.2-0.5) | 0.5% | 0.8% (0.4-1.4%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Italy | 17 | 73 (42-129) | 0.3 | 1.4 (0.8-2.5) | 0.3% | 1.4% (0.8-2.5%) |
| Jamaica | 2 | 2 (1-3) | 1.0 | 0.8 (0.5-1.5) | 1.4% | 1.2% (0.6-2.1%) |
| Japan | 45 | 97 (53-180) | 0.4 | 0.9 (0.5-1.6) | 0.6% | 1.2% (0.7-2.3%) |
| Jordan | 0 | 0 (0-1) | 0.0 | 0.1 (0-0.2) | 0% | 0.3% (0.1-0.8%) |
| Kiribati | 0 | 0 (0-0) | 0.0 | 2.6 (0.7-9.6) | 0% | 2.2% (0.6-8.1%) |
| Kuwait | 0 | 0 (0-0) | 0.0 | 0.1 (0-0.2) | 0% | 0.3% (0.1-0.9%) |
| Kyrgyzstan | 271 | 15 (11-20) | 67.3 | 3.6 (2.6-5.1) | 67.9% | 3.7% (2.6-5.1%) |
| Latvia | 271 | 120 (72-203) | 159.5 | 70.8 (42.1-119.3) | 33.9% | 15% (8.9-25.3%) |
| Lithuania | 95 | 267 (119-402) | 38.0 | 107 (47.8-160.9) | 20.2% | 56.7% (25.4-85.3%) |
| Luxembourg | 0 | 7 (2-20) | 0.0 | 14.3 (5.1-42) | 0% | 19.5% (7-57.2%) |
| Maldives | 0 | 0 (0-0) | 0.0 | 0.3 (0.1-1) | 0% | 1.1% (0.3-3.4%) |
| Malta | 1 | 1 (0-2) | 2.8 | 2.4 (1.1-5.4) | 5.9% | 4.9% (2.2-11.2%) |
| Mauritius | 0 | 1 (0-2) | 0.0 | 0.7 (0.4-1.4) | 0% | 1.1% (0.5-2.1%) |
| Mexico | 37 | 19 (12-32) | 0.4 | 0.2 (0.1-0.4) | 2% | 1.1% (0.7-1.8%) |
| Morocco | 0 | 4 (2-10) | 0.0 | 0.2 (0.1-0.4) | 0% | 0.2% (0.1-0.5%) |
| Netherlands | 17 | 37 (24-61) | 1.2 | 2.6 (1.7-4.3) | 1.3% | 2.9% (1.9-4.8%) |
| New Zealand | 15 | 20 (12-33) | 4.3 | 5.5 (3.4-9.3) | 6% | 7.9% (4.8-13.2%) |
| Nicaragua | 0 | 2 (1-3) | 0.0 | 0.5 (0.3-0.8) | 0% | 1.3% (0.8-2.4%) |
| Norway | 9 | 8 (4-18) | 2.1 | 1.8 (0.9-4.3) | 4.2% | 3.5% (1.7-8.5%) |
| Oman | 0 | 0 (0-1) | 0.0 | 0.1 (0-0.3) | 0% | 0.4% (0.2-0.9%) |
| Panama | 0 | 8 (6-12) | 0.0 | 2.9 (2-4.3) | 0% | 3.7% (2.5-5.4%) |
| Paraguay | 1 | 6 (4-9) | 0.2 | 1.3 (0.8-2) | 0.5% | 2.7% (1.7-4.1%) |
| Peru | 0 | 13 (8-21) | 0.0 | 0.6 (0.4-1) | 0% | 1.4% (0.9-2.2%) |
| Philippines | 15 | 39 (24-65) | 0.2 | 0.6 (0.4-1.1) | 0.5% | 1.3% (0.8-2.1%) |
| Poland | 415 | 576 (314-1,060) | 12.6 | 17.5 (9.6-32.3) | 3.3% | 4.6% (2.5-8.4%) |
| Portugal | 15 | 61 (38-100) | 1.7 | 6.9 (4.3-11.1) | 2.3% | 9.4% (5.9-15.3%) |
| Republic of Korea | 1 | 57 (37-91) | 0.0 | 1.6 (1.1-2.6) | 0.1% | 3.8% (2.5-6.1%) |
| Republic of Moldova | 125 | 212 (96-327) | 36.5 | 61.9 (27.9-95.4) | 28.4% | 48.2% (21.7-74.3%) |
| Romania | 70 | 342 (194-622) | 4.2 | 20.6 (11.7-37.5) | 1.8% | 9% (5.1-16.4%) |
| Russian Federation | 19,749 | 8,634 (3,205-24,021) | 163.8 | 71.6 (26.6-199.2) | 26.7% | 11.7% (4.3-32.5%) |
| Saint Kitts and Nevis | 0 | 0 (0-1) | 0.0 | 6.6 (1.8-24.7) | 0% | 9.1% (2.5-34%) |
| Saint Lucia | 4 | 2 (1-5) | 28.9 | 14.7 (6.6-34) | 16% | 8.1% (3.7-18.8%) |
| Saint Vincent and the Grenadines | 0 | 0 (0-1) | 0.0 | 4 (1.6-10.5) | 0% | 6.6% (2.6-17.3%) |
| Saudi Arabia | 0 | 2 (1-6) | 0.0 | 0.1 (0-0.3) | 0% | 0.2% (0.1-0.5%) |
| Serbia | 20 | 596 (333-1,063) | 2.7 | 80.4 (45-143.5) | 0.1% | 4% (2.2-7.1%) |
| Singapore | 2 | 1 (0-2) | 0.4 | 0.2 (0.1-0.5) | 0.8% | 0.5% (0.2-1%) |
| Slovakia | 99 | 38 (24-60) | 21.5 | 8.2 (5.2-13) | 27.6% | 10.5% (6.7-16.6%) |
| Slovenia | 60 | 60 (30-121) | 34.0 | 33.9 (17.3-68.6) | 16.3% | 16.2% (8.3-32.9%) |
| Spain | 26 | 147 (87-258) | 0.7 | 3.7 (2.2-6.6) | 0.6% | 3.1% (1.8-5.5%) |
| Sri Lanka | 6 | 3 (2-7) | 0.4 | 0.2 (0.1-0.5) | 0.8% | 0.5% (0.2-0.9%) |
| Suriname | 0 | 2 (1-3) | 0.0 | 4 (1.9-8.7) | 0% | 3.7% (1.8-8%) |
| Sweden | 26 | 21 (12-44) | 3.2 | 2.7 (1.6-5.4) | 4.7% | 3.8% (2.2-7.8%) |
| Switzerland | 16 | 63 (38-106) | 2.3 | 9 (5.5-15.3) | 1.8% | 7% (4.3-11.8%) |
| Thailand | 0 | 35 (21-60) | 0.0 | 0.7 (0.4-1.2) | 0% | 1.1% (0.6-1.8%) |
| Trinidad and Tobago | 2 | 2 (1-4) | 1.9 | 2.2 (1.3-3.8) | 2.6% | 3% (1.7-5.1%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Tunisia | 0 | 2 (1-5) | 0.0 | 0.3 (0.1-0.7) | 0% | 0.3% (0.1-0.7%) |
| Turkey | 2 | 9 (4-20) | 0.0 | 0.2 (0.1-0.4) | 0.1% | 0.3% (0.1-0.6%) |
| United Kingdom | 102 | 168 (90-390) | 1.9 | 3.2 (1.7-7.4) | 3.5% | 5.7% (3-13.2%) |
| United States of America | 526 | 628 (278-1,466) | 2.0 | 2.4 (1.1-5.7) | 1.7% | 2% (0.9-4.6%) |
| Uruguay | 2 | 24 (15-38) | 0.7 | 9 (5.7-14.2) | 0.6% | 7.3% (4.7-11.6%) |
| Venezuela (Bolivarian Republic of) | 6 | 16 (11-22) | 0.3 | 0.7 (0.5-1.1) | 0.9% | 2.4% (1.7-3.5%) |

Note: ACM = alcoholic cardiomyopathic deaths according to ICD-10 (code I42.6). Mortality rate = number of deaths per 1,000,000 adult population. Alcohol-attributable fraction = proportion of ACM deaths among all deaths due to CM. In highlighted countries, recorded ACM deaths are lower than lower CI of predicted ACM deaths.

**Table B.5** Comparison of alcoholic cardiomyopathy mortality data from vital registries/ model predictions and from the Global Burden of Disease study

| Country | Vital registry/ model prediction | GBD estimate |
|---|---|---|
| Afghanistan | 2.1 | 70.0 |
| Albania | 11.9 | 17.8 |
| Algeria | 7.0 | 89.0 |
| Andorra | 1.6 | 0.7 |
| Angola | 25.2 | 43.5 |
| Antigua and Barbuda * | 0.0 | 0.3 |
| Argentina * | 8.0 | 143.9 |
| Armenia | 1.4 | 14.9 |
| Australia * | 58.0 | 370.3 |
| Austria * | 12.0 | 148.3 |
| Azerbaijan | 2.2 | 147.3 |
| Bahamas * | 0.0 | 5.9 |
| Bahrain | 0.3 | 1.4 |
| Bangladesh | 1.2 | 44.1 |
| Barbados * | 0.0 | 4.3 |
| Belarus | 402.7 | 240.3 |
| Belgium * | 23.0 | 107.0 |
| Belize * | 0.0 | 1.2 |
| Benin | 2.1 | 11.9 |
| Bhutan | 0.1 | 0.4 |
| Bolivia (Plurinational State of) * | 0.0 | 5.9 |
| Bosnia and Herzegovina | 50.8 | 99.9 |
| Botswana | 5.0 | 10.5 |
| Brazil * | 259.0 | 1,472.1 |
| Brunei Darussalam | 0.1 | 7.5 |
| Bulgaria * | 8.0 | 26.0 |
| Burkina Faso | 17.9 | 26.2 |
| Burundi | 8.5 | 23.2 |
| Cabo Verde | 0.4 | 0.5 |
| Cambodia | 7.6 | 55.3 |
| Cameroon | 29.3 | 42.7 |
| Canada * | 59.0 | 386.8 |
| Central African Republic | 1.8 | 11.9 |
| Chad | 1.6 | 11.6 |
| Chile * | 13.0 | 56.5 |
| China | 237.1 | 2,688.8 |
| Colombia * | 0.0 | 26.2 |
| Comoros | 0.2 | 0.8 |
| Congo | 5.1 | 10.0 |
| Cook Islands | 0.2 | NA |
| Costa Rica * | 5.0 | 14.0 |
| Cote d'Ivoire | 28.4 | 38.6 |
| Croatia * | 39.0 | 235.0 |
| Cuba * | 84.0 | 321.2 |

| | | |
|---|---|---|
| Cyprus * | 1.0 | 3.0 |
| Czechia * | 24.0 | 90.0 |
| Democratic People's Republic of Korea | 4.6 | 33.2 |
| Democratic Republic of the Congo | 8.2 | 84.3 |
| Denmark * | 6.0 | 44.1 |
| Djibouti | 0.2 | 1.3 |
| Dominica * | 0.0 | 0.6 |
| Dominican Republic * | 1.0 | 14.2 |
| Ecuador * | 2.0 | 12.0 |
| Egypt | 18.0 | 234.1 |
| El Salvador * | 0.0 | 2.7 |
| Equatorial Guinea | 6.3 | 2.8 |
| Eritrea | 0.6 | 6.4 |
| Estonia * | 73.0 | 101.6 |
| Ethiopia | 9.6 | 123.9 |
| Fiji * | 0.0 | 2.8 |
| Finland * | 88.0 | 228.1 |
| France * | 101.0 | 421.7 |
| Gabon | 9.2 | 6.1 |
| Gambia | 0.6 | 1.2 |
| Georgia * | 2.0 | 18.0 |
| Germany * | 490.0 | 3,496.5 |
| Ghana | 6.6 | 90.6 |
| Greece * | 7.0 | 27.2 |
| Grenada * | 0.0 | 1.3 |
| Guatemala * | 0.0 | 8.0 |
| Guinea | 1.0 | 11.0 |
| Guinea-Bissau | 0.7 | 2.9 |
| Guyana * | 1.0 | 7.4 |
| Haiti * | 0.0 | 63.5 |
| Honduras * | 0.0 | 6.5 |
| Hungary * | 221.0 | 1,277.3 |
| Iceland * | 1.0 | 0.7 |
| India | 86.6 | 730.4 |
| Indonesia | 13.0 | 1,346.9 |
| Iran (Islamic Republic of) | 4.5 | 65.4 |
| Iraq | 3.1 | 73.5 |
| Ireland * | 11.0 | 49.3 |
| Israel * | 1.0 | 5.9 |
| Italy * | 17.0 | 118.8 |
| Jamaica * | 2.0 | 18.0 |
| Japan * | 45.0 | 281.4 |
| Jordan * | 0.0 | 2.3 |
| Kazakhstan | 33.9 | 1,036.7 |
| Kenya | 4.8 | 62.2 |
| Kiribati * | 0.0 | 0.2 |
| Kuwait * | 0.0 | 1.7 |
| Kyrgyzstan * | 271.0 | 273.2 |

| | | |
|---|---|---|
| Lao People's Democratic Republic | 13.6 | 31.4 |
| Latvia * | 271.0 | 364.6 |
| Lebanon | 1.2 | 10.0 |
| Lesotho | 2.0 | 13.1 |
| Liberia | 1.7 | 4.1 |
| Libya | 0.9 | 11.6 |
| Lithuania * | 95.0 | 240.5 |
| Luxembourg * | 0.0 | 4.2 |
| Madagascar | 3.1 | 60.2 |
| Malawi | 2.6 | 17.2 |
| Malaysia | 2.9 | 67.4 |
| Maldives * | 0.0 | 0.3 |
| Mali | 1.5 | 10.0 |
| Malta * | 1.0 | 1.7 |
| Marshall Islands | 0.1 | 0.2 |
| Mauritania | 0.3 | 2.6 |
| Mauritius * | 0.0 | 5.7 |
| Mexico * | 37.0 | 173.1 |
| Micronesia (Federated States of) | 0.2 | 0.5 |
| Monaco | 2.2 | NA |
| Mongolia | 4.7 | 14.9 |
| Montenegro | 9.3 | 114.6 |
| Morocco * | 0.0 | 68.7 |
| Mozambique | 3.2 | 31.7 |
| Myanmar | 18.6 | 302.3 |
| Namibia | 8.9 | 8.2 |
| Nauru | NA | NA |
| Nepal | 0.9 | 9.1 |
| Netherlands * | 17.0 | 151.2 |
| New Zealand * | 15.0 | 89.7 |
| Nicaragua * | 0.0 | 9.3 |
| Niger | 0.9 | 12.5 |
| Nigeria | 502.2 | 166.9 |
| Niue | NA | NA |
| Norway * | 9.0 | 30.4 |
| Oman * | 0.0 | 7.3 |
| Pakistan | 3.1 | 97.0 |
| Palau | 0.0 | NA |
| Panama * | 0.0 | 7.8 |
| Papua New Guinea | 1.8 | 25.3 |
| Paraguay * | 1.0 | 9.9 |
| Peru * | 0.0 | 13.7 |
| Philippines * | 15.0 | 422.9 |
| Poland * | 415.0 | 1,750.9 |
| Portugal * | 15.0 | 76.5 |
| Qatar | 0.1 | 1.3 |
| Republic of Korea * | 1.0 | 72.8 |
| Republic of Moldova * | 125.0 | 158.7 |

| | | |
|---|---|---|
| Romania * | 70.0 | 899.1 |
| Russian Federation * | 19,749.0 | 46,546.2 |
| Rwanda | 16.1 | 17.3 |
| Saint Kitts and Nevis * | 0.0 | NA |
| Saint Lucia * | 4.0 | 3.4 |
| Saint Vincent and the Grenadines * | 0.0 | 1.2 |
| Samoa | 0.2 | 0.6 |
| San Marino | 0.5 | NA |
| Sao Tome and Principe | 0.3 | 0.2 |
| Saudi Arabia * | 0.0 | 66.7 |
| Senegal | 0.9 | 9.8 |
| Serbia * | 20.0 | 793.5 |
| Seychelles | 1.3 | 3.3 |
| Sierra Leone | 3.5 | 8.5 |
| Singapore * | 2.0 | 7.1 |
| Slovakia * | 99.0 | 89.5 |
| Slovenia * | 60.0 | 42.9 |
| Solomon Islands | 0.3 | 2.2 |
| Somalia | 0.7 | 11.4 |
| South Africa | 148.8 | 342.6 |
| Spain * | 26.0 | 204.9 |
| Sri Lanka * | 6.0 | 150.9 |
| Sudan | 4.4 | 83.6 |
| Suriname * | 0.0 | 2.1 |
| Swaziland | 7.0 | 5.0 |
| Sweden * | 26.0 | 107.4 |
| Switzerland * | 16.0 | 91.9 |
| Syrian Arab Republic | 2.7 | 22.1 |
| Tajikistan | 1.6 | 52.5 |
| Thailand * | 0.0 | 35.0 |
| The former Yugoslav Republic of Macedonia | 72.8 | 273.3 |
| Timor-Leste | 0.3 | 2.8 |
| Togo | 1.6 | 8.0 |
| Tonga | 0.1 | 0.1 |
| Trinidad and Tobago * | 2.0 | 9.7 |
| Tunisia * | 0.0 | 25.3 |
| Turkey * | 2.0 | 35.9 |
| Turkmenistan | 3.4 | 128.5 |
| Tuvalu | NA | NA |
| Uganda | 35.9 | 61.9 |
| Ukraine | 290.9 | 2,121.8 |
| United Arab Emirates | 1.5 | 25.7 |
| United Kingdom * | 102.0 | 511.0 |
| United Republic of Tanzania | 50.7 | 91.3 |
| United States of America * | 526.0 | 5,645.7 |
| Uruguay * | 2.0 | 49.5 |
| Uzbekistan | 2.5 | 21.2 |

| | | |
|---|---|---|
| Vanuatu | 0.1 | 1.1 |
| Venezuela (Bolivarian Republic of) * | 6.0 | 109.4 |
| Viet Nam | 18.1 | 428.4 |
| Yemen | 2.7 | 39.5 |
| Zambia | 3.5 | 34.2 |
| Zimbabwe | 7.5 | 41.1 |

Note: Vital registry mortality data refers to either directly sourced (indicated with an asterisk *) or model predictions, which represent the main results of this study. In highlighted countries, ACM deaths in vital registries are larger than the GBD estimates.

# 11 Appendix C (study III)

The following additional file was published together with the study (for access: https://www.mdpi.com/2077-0383/8/8/1137):

**Additional file C.1:** Country-level data for key variables including source years.

## 11.1 Methods

### 11.1.1 Definition of cause of death categories

In **Table C.1**, the disease definitions for all CVD (including garbage codes), CVD (excluding garbage codes), all CM, ACM, and cardiovascular as well as HF garbage codes are presented. The table lists ICD-10 cause of deaths codes matched with mortality data obtained from the WHO.

### 11.1.2 Description of sensitivity analyses

In the GBD study, a redistribution model is applied to estimate so called redistribution proportions, which are employed for redistributing garbage coded deaths to other diseases. In this study, we performed a similar model building on the hypotheses that among all cardiovascular deaths, the proportion of deaths with HF garbage codes is negatively associated with the proportion of ACM deaths.

For the sensitivity analyses, we used all mortality data from all available years, i.e. from 823 country-years (for details, see Additional file 2). The denominator for calculating HF garbage code and ACM proportions was 'all CVD' and was calculated from the sum of all registered deaths from CVD and CVD garbage codes (for definition, see **Table C.1**). Prior to building regression models, the data structure of the dependent variable (% of ACM deaths) was examined using scatter plots and bivariate correlations with % of HF garbage code deaths and alcohol exposure (for results see **Table C.2**).

**Table C.1** Cause of death definition

| GBD cause of death definition | ICD-10 cause of death codes | Short term used in manuscript |
|---|---|---|
| All cardiovascular diseases (sum of garbage and non-garbage codes) | Non-garbage:<br>B33.2, G45-G46.8, I01-I01.9, I02.0, I05-I09.9, I11-I11.9, I20-I25.9, I28-I28.8, I30-I31.1, I31.8-I37.8, I38-I41.9, I42.1-I42.8, I43-I43.9, I47-I48.9, I51.0-I51.4, I60-I63.9, I65-I66.9, I67.0-I67.3, I67.5-I67.6, I68.0-I68.2, I69.0-I69.3, I70.2-I70.8, I71-I73.9, I77-I83.9, I86-I89.0, I89.9, I98, K75.1<br>Garbage:<br>*Level-1:* I26-I26.9, I31.2-I31.4, I37.9, I46-I46.9, I50-I50.9, I51.7, I67.4, I76, I95-I95.1, I95.8-I95.9,<br>*Level-2:* I10-I10.9, I15-I15.9, I27-I27.0, I27.2-I27.9, I28.9, I70-I70.1, I70.9, I74-I75.8<br>*Level-3:* I00.0, I03-I04., I14-I14., I16-I19, I29-I29.9, I44-I45.9, I49-I49.9, I51, I51.6, I51.8-I59, I90-I94, I96-I96.9, I98.4-I98.8, I99<br>*Level-4:* I42-I42.0, I42.9, I51.5, I64-I64.9, I67, I67.8-I68, I68.8-I69, I69.4-I69.9 | All CVD |
| Cardiovascular diseases | B33.2, G45-G46.8, I01-I01.9, I02.0, I05-I09.9, I11-I11.9, I20-I25.9, I28-I28.8, I30-I31.1, I31.8-I37.8, I38-I41.9, I42.1-I42.8, I43-I43.9, I47-I48.9, I51.0-I51.4, I60-I63.9, I65-I66.9, I67.0-I67.3, I67.5-I67.6, I68.0-I68.2, I69.0-I69.3, I70.2-I70.8, I71-I73.9, I77-I83.9, I86-I89.0, I89.9, I98, K75.1 | CVD |
| Cardiomyopathy and myocarditis | B33.2, I40-I41.9, I42.1-I42.8, I43-I43.9, I51.4 | All cardiomyopathies |
| Alcoholic cardiomyopathy | I42.6 | ACM |
| Garbage codes in ICD-10 category of circulatory diseases | *Level-1:* I26-I26.9, I31.2-I31.4, I37.9, I46-I46.9, I50-I50.9, I51.7, I67.4, I76, I95-I95.1, I95.8-I95.9,<br>*Level-2:* I10-I10.9, I15-I15.9, I27-I27.0, I27.2-I27.9, I28.9, I70-I70.1, I70.9, I74-I75.8<br>*Level-3:* I00.0, I03-I04., I14-I14., I16-I19, I29-I29.9, I44-I45.9, I49-I49.9, I51, I51.6, I51.8-I59, I90-I94, I96-I96.9, I98.4-I98.8, I99<br>*Level-4:* I42-I42.0, I42.9, I51.5, I64-I64.9, I67, I67.8-I68, I68.8-I69, I69.4-I69.9 | CVD garbage codes |
| Heart failure garbage codes | I50 | HF garbage code |

Note: Mapping of ICD-10 codes to disease category obtained from GBD 2017 study.

**Table C.2** Bivariate correlations of % heart failure garbage codes and % alcoholic cardiomyopathy mortality

| | | 15-49 year olds | | | 50-64 year olds | | | 65+ year olds | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **% ACM** | **% HF Garbage codes** | **APC** | **% ACM** | **% HF Garbage codes** | **APC** | **% ACM** | **% HF Garbage codes** | **APC** |
| Women | % ACM | 1 | | | 1 | | | 1 | | |
| | % HF Garbage codes | -.15 | 1 | | -.24 | 1 | | -.19 | 1 | |
| | APC | .26 | -.17 | 1 | .34 | -.14 | 1 | .21 | -.01 | 1 |
| Men | % ACM | 1 | | | 1 | | | 1 | | |
| | % HF Garbage codes | -.24 | 1 | | -.29 | 1 | | -.21 | 1 | |
| | APC | .30 | -.15 | 1 | .35 | -.15 | 1 | .21 | -.10 | 1 |

Note: ACM = Alcoholic cardiomyopathy. HF = Heart failure. APC = Alcohol per capita consumption. Bivariate correlations based on mortality data from 823 country-years with available civil registry mortality data. Proportion of deaths are calculated from the denominator of all CVD deaths (including garbage codes).

Between ACM and HF, the distribution of deaths across age groups were substantially different. Among 50 to 64 year olds, the largest share of ACM deaths (47%) but only a fraction of HF garbage code deaths (7%) have been registered. This pattern reversed for the older age groups (65 years and older), among which 29% of all ACM deaths but 91% of all deaths assigned with HF garbage codes have been registered. Further and as illustrated in **Figure C.1**, the association of % ACM deaths and % HF garbage code deaths varied largely across sex and age. Consequently, all regression models were stratified by sex and age group (15-49, 50-64, 65+).

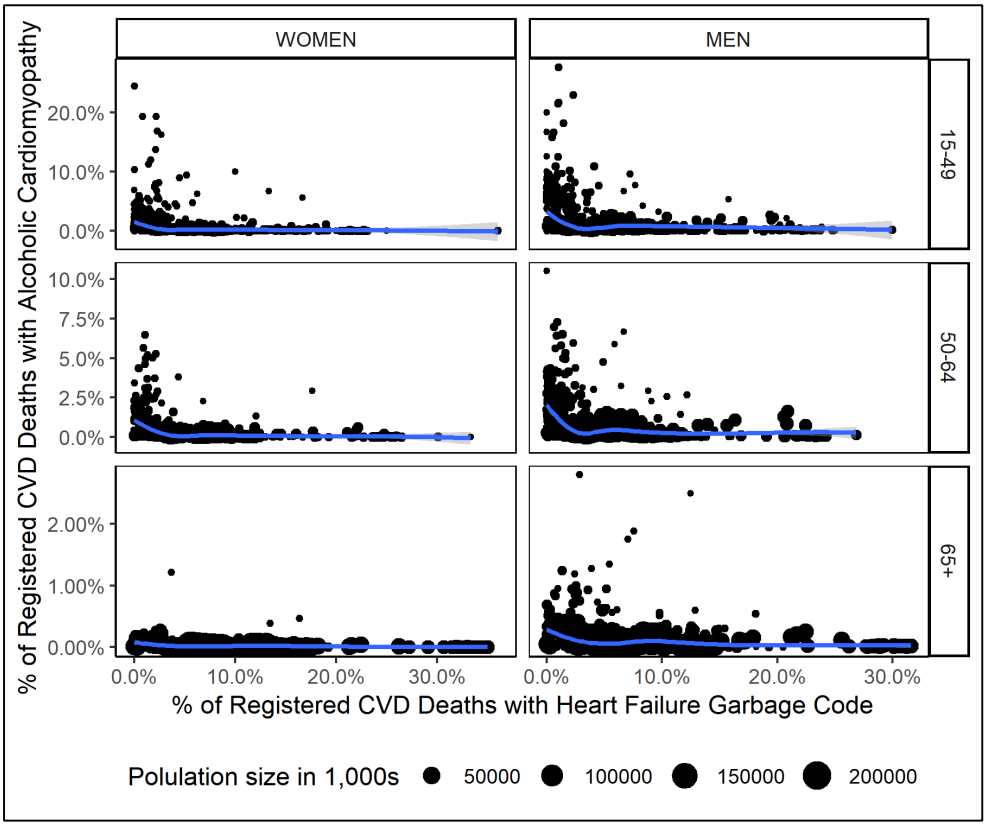


**Figure C.1** Scatter plots of % heart failure garbage code deaths and % alcoholic cardiomyopathy deaths among all cardiovascular disease deaths by sex and age group; the blue line denotes a weighted smoothing function of the two variables.

For each stratum, we fitted the following models: 1A) a fractional response model with a linear combination of both covariates (% HF garbage code deaths and APC) and allowing for random intercepts for each country; 1B) a Poisson regression where the dependent variable was multiplied with 10,000 and rounded to the nearest integer and with the same covariate structure as in 1A); 2A) a fractional response regression as in 1A but with an additional set of 3rd order orthogonal polynomials of % HF garbage code deaths (as suggested by scatter plots, see Appendix Figure 1); 2B) a Poisson regression as in 1B but with an additional set of 3rd order orthogonal polynomials of % HF garbage code deaths. Poisson regression models (1B and 2B) were found to be superior to fractional response models in terms of data fit as assessed using $R^2$ and plotting fitted and observed data. Subsequently, Poisson models with linear and polynomial covariates were compared within each stratum using analysis of deviance tests. For most strata, model 2B (random effects Poisson regression with 3rd order polynomials of % HF garbage code deaths) were found the best fitting model ($Chi^2$-tests: $p<.001$ for all tests), except young females, for which model 1B indicated best fit (random effects Poisson regression with linear combination of covariates).

For the random effects Poisson regression models, the equation is written as generalized linear model and was performed by sex and three age groups (15-49, 50-64, 65+):

$$ACM_c = f(\alpha + \beta_1 HF + \beta_2 HF^2 + \beta_3 HF^3 + \beta_4 APC + \gamma_c + \varepsilon_c)$$

Where:

*f()* = Poisson function with log link function and Poisson distributed data
$ACM_c$ = percentage of all cardiovascular deaths which were coded to alcohol cardiomyopathy, by country
$\alpha$ = constant
*HF* = percentage of all cardiovascular deaths which were coded to heart failure
$\beta_1$ = slope coefficient describing the association between HF and $ACM_c$
$\beta_2$ = slope coefficient describing the association between the polynomial $HF^2$ and $ACM_c$ (not included among young females)
$\beta_3$ = slope coefficient describing the association between the polynomial $HF^3$ and $ACM_c$ (not included among young females)
*APC* = Alcohol per capita consumption
$\beta_4$ = slope coefficient describing the association between APC and $ACM_c$
$\gamma_r$ = country-specific random intercept
$\varepsilon_c$ = standard error

For comparison, the regression equation used in the GBD study to calculate redistribution proportions is as follows (for details, see Appendix 1 of (Roth et al., 2018)):

$$TG_{crt} = \alpha + \beta_1 Gar_{crt} + \beta_2 Age_{crt} Gar_{crt} + \theta_r Gar_{crt} + \gamma_r + \varepsilon_{ct}$$

Where:

$TG_{crt}$ = percentage of deaths within the given garbage code's universe which were coded to a given target group, by country
$\alpha$ = constant
$Gar_{crt}$ = percentage of deaths within the given garbage code's universe which were coded to a given set of garbage codes
$\beta_1$ = slope coefficient describing the association between $Gar_{crt}$ and $TG_{crt}$
$\beta_2$ = slope coefficient describing the association between the interaction $Age_{crt}$ and $Gar_{crt}$
$\gamma_r$ = region-specific random intercept (or super-region if the random effect on region is not significant)
$\vartheta_r$ = region-specific random slope (or super-region if the random effect on region is not significant)
$\varepsilon_{ct}$ = standard error, normally distributed and calculated by bootstrapping

There are two main differences between the GBD redistribution model and the model presented in this study. First, we accounted for alcohol exposure as the core determinant for ACM and second, allowed for a non-linear relationship between HF garbage code and ACM mortality proportions.

## 11.2 Results

### 11.2.1 Mortality rates of registered and estimated deaths

In **Table C.3**, **Table C.4** and **Table C.5**, the mortality rates of CVD, all CM, and ACM are presented by sex and age. The table also includes the ratio of estimated to registered mortality rates, which are largely constant for CVD but increase with age for all CM and ACM.

**Table C.3** Mortality rates of registered and estimated deaths of alcoholic cardiomyopathies by sex and age

| | Women | | | Men | | | Both sexes | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Registered** | **Estimated** | **Ratio** | **Registered** | **Estimated** | **Ratio** | **Registered** | **Estimated** | **Ratio** |
| 15-19 | 0.00 | 0.01 | NA | 0.00 | 0.03 | NA | 0.00 | 0.02 | NA |
| 20-24 | 0.00 | 0.02 | NA | 0.01 | 0.06 | 6.6 | 0.00 | 0.04 | 8.5 |
| 25-29 | 0.01 | 0.03 | 3.9 | 0.04 | 0.16 | 3.5 | 0.03 | 0.10 | 3.6 |
| 30-34 | 0.01 | 0.06 | 5.3 | 0.11 | 0.36 | 3.3 | 0.06 | 0.21 | 3.5 |
| 35-39 | 0.01 | 0.09 | 6.7 | 0.23 | 0.68 | 3.0 | 0.12 | 0.39 | 3.2 |
| 40-44 | 0.05 | 0.17 | 3.4 | 0.34 | 1.25 | 3.7 | 0.19 | 0.71 | 3.7 |
| 45-49 | 0.10 | 0.31 | 3.1 | 0.56 | 2.04 | 3.6 | 0.33 | 1.17 | 3.6 |
| 50-54 | 0.10 | 0.46 | 4.7 | 0.83 | 3.10 | 3.7 | 0.46 | 1.76 | 3.8 |
| 55-59 | 0.16 | 0.73 | 4.6 | 1.00 | 4.70 | 4.7 | 0.57 | 2.66 | 4.7 |
| 60-64 | 0.22 | 0.95 | 4.2 | 1.16 | 6.02 | 5.2 | 0.67 | 3.38 | 5.0 |
| 65-69 | 0.14 | 1.03 | 7.2 | 1.14 | 6.88 | 6.0 | 0.61 | 3.79 | 6.2 |
| 70-74 | 0.14 | 1.15 | 8.3 | 0.95 | 7.96 | 8.4 | 0.51 | 4.26 | 8.4 |
| 75-79 | 0.09 | 1.32 | 15.5 | 0.69 | 8.80 | 12.7 | 0.35 | 4.58 | 13.1 |
| 80-84 | 0.09 | 1.44 | 15.4 | 0.56 | 8.59 | 15.2 | 0.28 | 4.32 | 15.2 |
| 85-99 | 0.05 | 2.39 | 45.5 | 0.32 | 9.50 | 29.4 | 0.14 | 4.72 | 33.4 |

Note: Mortality rates = deaths per 100,000 population. Ratio = ratio of estimated to registered deaths. Mortality data obtained from *N*=77 countries (see Additional file C.1).

**Table C.4** Mortality rates of registered and estimated deaths of cardiovascular diseases by sex and age

| | Women | | | Men | | | Both sexes | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Registered** | **Estimated** | **Ratio** | **Registered** | **Estimated** | **Ratio** | **Registered** | **Estimated** | **Ratio** |
| 15-19 | 1.3 | 2.8 | 2.2 | 2.1 | 4.1 | 1.9 | 1.7 | 3.5 | 2.0 |
| 20-24 | 1.9 | 4.1 | 2.1 | 3.8 | 6.6 | 1.7 | 2.9 | 5.3 | 1.8 |
| 25-29 | 3.0 | 5.8 | 1.9 | 6.1 | 10.3 | 1.7 | 4.6 | 8.1 | 1.8 |
| 30-34 | 4.9 | 9.2 | 1.9 | 10.6 | 17.5 | 1.7 | 7.7 | 13.4 | 1.7 |
| 35-39 | 8.7 | 15.3 | 1.8 | 19.0 | 30.0 | 1.6 | 13.8 | 22.7 | 1.6 |
| 40-44 | 15.5 | 26.0 | 1.7 | 36.0 | 53.9 | 1.5 | 25.7 | 39.9 | 1.6 |
| 45-49 | 26.7 | 43.9 | 1.6 | 63.6 | 94.3 | 1.5 | 45.0 | 68.9 | 1.5 |
| 50-54 | 43.4 | 71.2 | 1.6 | 109.8 | 162.1 | 1.5 | 76.0 | 116.0 | 1.5 |
| 55-59 | 70.1 | 114.5 | 1.6 | 176.3 | 265.9 | 1.5 | 121.8 | 188.2 | 1.6 |
| 60-64 | 112.6 | 188.1 | 1.7 | 270.1 | 414.3 | 1.5 | 188.0 | 296.4 | 1.6 |
| 65-69 | 181.5 | 304.2 | 1.7 | 386.3 | 600.0 | 1.6 | 278.1 | 443.8 | 1.6 |
| 70-74 | 320.1 | 549.8 | 1.7 | 588.2 | 950.7 | 1.6 | 442.5 | 732.9 | 1.7 |
| 75-79 | 604.2 | 1039.4 | 1.7 | 954.0 | 1552.5 | 1.6 | 756.8 | 1263.3 | 1.7 |
| 80-84 | 1162.5 | 2008.5 | 1.7 | 1632.0 | 2699.4 | 1.6 | 1351.4 | 2286.5 | 1.7 |
| 85-99 | 3112.1 | 5667.5 | 1.8 | 3538.3 | 6178.5 | 1.8 | 3251.8 | 5835.0 | 1.8 |

Note: Mortality rates = deaths per 100,000 population. Ratio = ratio of estimated to registered deaths. Mortality data obtained from *N*=77 countries (see Additional file C.1).

**Table C.5** Mortality rates of registered and estimated deaths of all cardiomyopathies by sex and age

| | Women | | | Men | | | Both sexes | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Registered** | **Estimated** | **Ratio** | **Registered** | **Estimated** | **Ratio** | **Registered** | **Estimated** | **Ratio** |
| 15-19 | 0.1 | 0.3 | 2.3 | 0.3 | 0.6 | 2.5 | 0.2 | 0.5 | 2.4 |
| 20-24 | 0.1 | 0.4 | 4.1 | 0.2 | 0.8 | 3.5 | 0.2 | 0.6 | 3.7 |
| 25-29 | 0.2 | 0.5 | 3.3 | 0.4 | 1.2 | 3.1 | 0.3 | 0.8 | 3.2 |
| 30-34 | 0.2 | 0.6 | 3.7 | 0.5 | 1.6 | 3.4 | 0.3 | 1.1 | 3.5 |
| 35-39 | 0.3 | 0.9 | 3.6 | 0.8 | 2.4 | 3.1 | 0.5 | 1.6 | 3.2 |
| 40-44 | 0.3 | 1.2 | 3.7 | 1.0 | 3.6 | 3.7 | 0.7 | 2.4 | 3.7 |
| 45-49 | 0.5 | 1.7 | 3.7 | 1.4 | 5.2 | 3.7 | 1.0 | 3.5 | 3.7 |
| 50-54 | 0.6 | 2.5 | 4.2 | 1.9 | 7.6 | 4.0 | 1.3 | 5.0 | 4.0 |
| 55-59 | 0.8 | 3.9 | 4.8 | 2.4 | 11.1 | 4.7 | 1.6 | 7.4 | 4.7 |
| 60-64 | 1.1 | 5.5 | 5.1 | 2.8 | 14.7 | 5.3 | 1.9 | 9.9 | 5.2 |
| 65-69 | 1.3 | 8.1 | 6.4 | 3.2 | 19.1 | 6.0 | 2.2 | 13.3 | 6.1 |
| 70-74 | 1.9 | 13.4 | 7.0 | 3.4 | 26.9 | 8.0 | 2.6 | 19.6 | 7.6 |
| 75-79 | 2.9 | 25.2 | 8.7 | 4.5 | 42.1 | 9.4 | 3.6 | 32.6 | 9.1 |
| 80-84 | 5.5 | 50.4 | 9.2 | 6.1 | 67.4 | 11.1 | 5.7 | 57.3 | 10.0 |
| 85-99 | 13.2 | 150.9 | 11.5 | 13.4 | 151.1 | 11.3 | 13.2 | 151.0 | 11.4 |

Note: Mortality rates = deaths per 100,000 population. Ratio = ratio of estimated to registered deaths. Mortality data obtained from *N*=77 countries (see Additional file C.1).

### 11.2.2 Sensitivity analyses: Alcoholic cardiomyopathy and heart failure deaths

Model results of random effects Poisson regressions are presented in **Table C.6**. Data fit of regression models was measured in the correlation between observed and fitted data, which was satisfactory (greater than .7) in the young- and middle-age strata and poorer in the oldest age group (correlation below .5). Further, the variation in the dependent variable (% of ACM deaths) was lowest in the oldest age group, most pronounced among females.

In post-hoc analyses, we examined characteristics of countries where the proportion of CVD deaths assigned with HF garbage codes was lower than 5%. A low share of HF garbage code deaths has been identified in 226 out of 823 country-years (27%) and has been associated with higher age-standardized estimated and registered mortality rates for CVD, all CM and ACM, as well as a lower population size ($p$<.001 for females and males, obtained from Poisson regressions). Further, a low share of HF garbage code deaths was linked to higher alcohol exposure among males ($p$<.001 from linear regression) but not among females ($p$=.019 from linear regression).

**Table C.6** Results of regression models on % alcoholic cardiomyopathy deaths among all cardiovascular disease deaths by age and sex

| | 15- to 49-years-old | | 50- to 64-years-old | | 65 years or older | |
|---|---|---|---|---|---|---|
| | **Women** | **Men** | **Women** | **Men** | **Women** | **Men** |
| Fixed effects (standard error) | | | | | | |
| Intercept | 1.11 (0.38)* | 3.43 (0.22)** | -0.03 (0.54) | 3.03 (0.2)** | -1.81 (0.48)** | 1.24 (0.26)** |
| First order polynomial of % HF garbage code deaths | 7.87 (0.48)** | 8.09 (0.27)** | 8.19 (0.53)** | 9.05 (0.21)** | 6.94 (1.08)** | 9.39 (0.31)** |
| Second order polynomial of % HF garbage code deaths [1] | / | 1.96 (0.2)** | 4.01 (0.41)** | 2.06 (0.15)** | 2.75 (1.26) | 2.49 (0.27)** |
| Third order polynomial of % HF garbage code deaths [1] | / | -3.3 (0.21)** | -3.03 (0.4)** | -3.92 (0.13)** | -4.63 (0.71)** | -2.21 (0.19)** |
| Alcohol *per capita* consumption | 0.02 (0.01) | 0.02 (0.002)** | -0.02 (0.01) | 0.01 (0.002)** | -0.04 (0.02) | -0.01 (0.003)** |
| Random effects | | | | | | |
| Standard deviation of country-level intercepts | 3.07 | 1.88 | 3.73 | 1.72 | 3.29 | 2.23 |
| R-square [2] | .772 | .815 | .868 | .732 | .333 | .475 |
| Mean (standard deviation) of dependent variable | 0.7% (2.1%) | 1.5% (2.9%) | 0.3% (0.7%) | 0.8% (1.2%) | 0.02% (0.06%) | 0.1% (0.2%) |

Note: All results from Poisson regressions (outcome multiplied by 10,000 and rounded to nearest integer) with random intercepts for each country. All models based on *N*=77 countries (823 country-years) with available mortality data from civil registries. ACM = alcoholic cardiomyopathy. CVD = Cardiovascular disease. HF = Heart failure. [1] The variable was centered around the sex- and age-specific mean. [2] R-square = square of the correlation coefficient between the actual and fitted values of the dependent variable. * $p$<=0.01 ; ** $p$<=0.001

# 12 Erklärung gemäß § 5 der Promotionsordnung

**Versicherung**

Hiermit versichere ich, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe; die aus fremden Quellen direkt oder indirekt übernommenen Gedanken sind als solche kenntlich gemacht. Die Arbeit wurde bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt.

Die vorgelegte Dissertation wurde unter wissenschaftlicher Betreuung von Prof. Hans-Ulrich Wittchen und Prof. Jürgen Rehm am Institut für Klinische Psychologie und Psychotherapie der Technischen Universität Dresden erstellt.

Es haben keine früheren erfolglosen Promotionsverfahren stattgefunden.

Die Promotionsordnung des Bereichs Mathematik und Naturwissenschaften der Technischen Universität Dresden, in der Fassung vom 23.02.2011, letzte Änderung 23.05.2018, wird anerkannt.

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Unterschrift, Datum